Public Assessment Report
for paediatric studies submitted in accordance with Article 45 of Regulation (EC) No1901/2006, as amended

Uniphyllin / Uniphyllin continus / Theophyllin Krugmann / Theophyllin Theodel / Theophylline Bruneau / Solosin / Solosin Retard / Solosin Retard Mite / Solosin Tropfen Theospirex retard Theo-dur Euphylong / Euphylong retard / Euphyllin / Euphyllin long / Euphyllin CR / Euphyllin CR N / Euphyllina / Euphyllina Rilcon / Respicur / Respicur retard Theostat / Theoplus

(Theophylline)

DK/W/0021/pdWS/001

Rapporteur:	Denmark
Finalisation procedure (day 120):	August 9, 2013
Date of finalisation of PAR	January 16, 2014

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ADMINISTRATIVE INFORMATION

Invented name of the medicinal product(s):	See section VI
INN (or common name) of the active substance(s):	Theophylline
MAH (s):	See section VI
Pharmaco-therapeutic group (ATC Code):	R03DA04
Pharmaceutical form(s) and strength(s):	Capsules 100 mg, 200 mg, 250 mg, 300 mg, 400 mg Sustained release capsules 100 mg, 125 mg, 200 mg, 250 mg, 300 mg, 375 mg, 400 mg, 500 mg Tablets 250 mg Coated tablets 250 mg Film-coated tablets 150 mg, 300 mg Prolonged-release tablets 100 mg, 135 mg, 200 mg, 250 mg, 270 mg, 300 mg. 400 mg, 600 mg Oral drops, solution 104 mg/ml Concentrate for solution for infusion 41.6 mg/ml Solution for injection 200 mg, 240 mg

I. EXECUTIVE SUMMARY

SmPC and PL changes are proposed in sections 4.1, 4.2, 4.3, 4.4 and 5.2.

Summary of outcome

☐ No change

☒ Change

☐ New study data: <section(s) xxxx, xxxx>

☐ New safety information: <section(s) xxxx, xxxx>

☒ Paediatric information clarified: section 4.2

☐ New indication: <section(s) xxxx, xxxx>

SmPC:
Section 4.1 Therapeutic indications
Theophylline should not be used as first drug of choice in the treatment of asthma in children.

Section 4.2 Posology and method of administration
Children below 6 months:
<Product name> should not be used in children below 6 months of age.

Solid dosage forms only:
Children below 6 years:
<Product name> should not be used in children below 6 years of age. Other dosage forms are available that are more suitable for children aged less than 6 years.

Section 4.3 Contraindications
Children under 6 months of age.

4.4 Special warnings:
In case of insufficient effect of the recommended dose and in case of adverse events, theophylline plasma concentration should be monitored.

Acute febrile illness
Fever decreases the clearance of theophylline. It may be necessary to decrease the dose to avoid intoxication.

5.2 Pharmacokinetic properties
Effective plasma concentrations: 5-12 µg/ml (do not exceed 20 µg/ml). Theophylline is mainly excreted by the kidneys.

RECOMMENDATION[1]

The outcome of the assessment of this article 45 submission regarding theophylline including the MAHs answers to the questions raised by the rapporteur (DK) and 3 CMSs (UK, NL, DE) is to recommend a harmonization process of the SmPCs with regard to paediatric dosing.

We recommend implementing a therapeutic interval of 5-12 µg/ml, with a note, that plasma concentration up to 20 µg/ml can be necessary to achieve efficacy in some cases. The product should not be administered to children below 6 months and the solid forms not to children below 6 years of age. The maintenance dose should be given in mg and plasma concentrations should be measured in case of insufficient effect of the recommended dose and in case of adverse events. Finally it should be implemented that fever may decrease the clearance of theophylline why it may be necessary to decrease the dose to avoid intoxication. Finally it should be added that theophylline is not first drug of choice in the treatment of asthma in children.

Recommendation
Type IB variation to be requested from the MAH by October 8, 2013.

II. INTRODUCTION

Theophylline is a methylxanthine, similar in structure to caffeine. Theophylline is a bronchodilator and has modest anti-inflammatory properties. Theophylline is indicated for treatment of bronchial asthma and chronic obstructive pulmonary disease and prevention of asthma attacks. The mechanism of action is not fully established. Its use for acute symptoms of asthma has been described since 1936 (68). Theophylline is only efficient after systemic administration, mostly as sustained-release preparations, but can also be administered intravenously. Studies with aminophylline are included; aminophylline is a stable mixture of theophylline and ethylenediamine with greater solubility in water. The use of theophylline is limited in children, in line with international and national clinical guidelines for asthma prevention and management (GINA 2010).

The pharmacokinetics, efficacy and safety of theophylline, also in children, are well-studied. Theophylline is rapidly and completely absorbed, and the bioavailability is close to 100 % when orally administered. Theophylline is extensively metabolised in the liver by CYP1A2, 2E1 and 3A4. Caffeine and 3-methylxanthine are active metabolites. The elimination half life is known to be considerably variable and ranges from 2 to 16 hours. Especially metabolism, but also volume of distribution is different in the various stages of childhood.

In accordance with Article 45 of the Regulation (EC) No 1901/2006, as amended on medicinal products for paediatric use, six MAHs have submitted relevant paediatric data concerning theophylline for assessment.

MAH 1 Mundipharma
MAH 2 Sanofi-Aventis
MAH 3 Gebro
MAH 4 Biophausia
MAH 5 Nycomed

[1] *The recommendation from section V can be copied in this section*.

MAH 6 Pierre Fabre

The MAHs have submitted 78 studies, including pharmacokinetic studies, efficacy and safety studies, reviews, metaanalyses and Cochrane reviews. Especially the pharmacokinetic studies are valuable and demonstrate important aspects of the developmental changes in the pharmacokinetic parameters during the various stages in childhood, whereas the clinical studies add less to the knowledge of theophylline.

Theophylline is a safe, well known, established treatment option in children with asthma when dosing (in steady state) is individualized based on serum theophylline concentrations. A study found a high correlation between saliva theophylline concentrations and blood concentration that could limit the need for blood samples in treatment with theophylline. The place in therapy of theophylline in children is and should be limited, which is also reflected in international and national guidelines. No new efficacy or safety information has emerged from the submitted studies, but it is clear that paediatric doses, recommended therapeutic interval and the paediatric indications vary considerably between SmPCs.
The pharmacokinetics of theophylline in premature neonates and newborn are well established, and the required dose lower than in older children due to undeveloped metabolism and therefore longer half live. Dosing to this special patient population is generally not addressed, even though the pharmacokinetics are pointed out and described in the SmPCs.
Annex 1 illustrates how the paediatric information is different in the various European SmPCs.

The outline of scientific discussion in this assessment report will follow *"the Rapporteur's Assessment Report template for paediatric studies submitted in accordance with Article 45 of Regulation (EC) No1901/2006"* and for each MAH's submission the following sections are included:

Information on the pharmaceutical formulation
Non-clinical aspects
Clinical aspects
Review of submitted clinical studies/reviews/study reports
MAH's conclusion
Assessor's discussion

The reports of the MAHs are quite diverse in form, substance and thoroughness. Surprisingly, only seven papers have been submitted by more than one MAH even though the majority of the references submitted are identified by search in the literature.

III. SCIENTIFIC DISCUSSION

III.1 MAH I (mundipharma)

III.2 Information on the pharmaceutical formulation.

MAH I has exclusively prolonged release tablet registered in European countries.
The lowest 12-hourly dose of theophylline prolonged release tablet is 200 mg. The recommended maintenance dose of 9 mg/kg therefore requires a minimum body weight of approximately 22 kg, which corresponds to the average weight of a 6-7 year old child. Additionally, given the prolonged-release nature of the MAH's products (has to be swallowed in one piece), they are not recommended for use in children under 5 years.

III.3 Non-clinical aspects

No non-clinical studies were submitted by the MAH.

III.4 Clinical aspects

1. Introduction
   1. Pharmacokinetic studies
      Literature review
      a. Premature neonates – 3 studies
      b. Age range 0-16 years – 18 studies
      c. Review article – 1
   2. Clinical studies in children
      Company sponsored clinical studies – 1 study (age 5 – 90 years)
      Trials from published literature – 7 studies

<u>Pharmacokinetic studies</u>

1.a Premature neonates

Du Preez et al. 1999 (15)
Title: *The pharmacokinetics of theophylline in premature neonates during the first few days after birth.*

Description
A South African study to estimate the pharmacokinetic parameters, clearance rate (CL). and volume of distribution (Vd) of theophylline in premature neonates and to identify factors contributing to inter-individual variability

Methods
Objective(s):
To investigate the population pharmacokinetics of theophylline in premature, apneic neonates within the first week of life.

Study design:
Pharmacokinetic study.
Study population /Sample size:

Any premature neonate under 2 days old,for whom theophylline was prescribed to reduce neonatal apnea.
A total of 105 premature black neonates.

Treatments
IV-aminophylline. Loading doses varied from 4-7.7 mg/kg. Maintenance doses ranged from 1.4--6 mg/kg per day and were given in 2-4 divided doses.

Outcomes/endpoints:
Serum theophylline concentrations 1 hour after loading dose and at day I, 2, and 3 (trough value).
Clearance and volume of distribution. Interoccasion and interindividial variability.
Statistical Methods:
NONMEM - Nonlinear mixed effects model.

Results
Recruitment/ Number analysed
A total of 263 serum concentrations from 105 premature black neonates.
Baseline data: Birth weight mean (SD) 1.3 kg (0.3). Gestational age mean (SD) 30.8 weeks (1.8). Postnatal age mean (SD) 1.1 days (0.3)

Efficacy results:
Clearance of theophylline was low (0.0056 and 0.0084 l/h/kg in patients without and with oxygen support respectively). T½ 76 and 56 hours respectively. Vd 0,63 L/kg. High interoccasion and interindividial variability 35 and 47 %.

Safety results:
Difficult to predict concentrations with the same degree of accuracy as in other populations.

Conclusion
Theophylline has a low clearance in premature neonates and a high inter-individual variability makes it difficult to predict doses.

Assessor's comments:
A valuable study of the pharmacokinetics of theophylline in premature neonates due to the large sample size of 105 patients. Clearance is low in premature neonates. This is well known and is already described in section 5.1.

Giacoia et al. 1976 (18)
Title: *Theophylline pharmacokinetics in premature infants with apnea.*

Description/objectives
A study to examine the pharmacokinetics of theophylline in low-birth-weight infants.

Methods
Study design:
Descriptive pharmakokinetic study.

Study population /Sample size:

Eight low-birth-weight infants treated for primary apnea and with no secondary diseases.

Treatments
Theophylline in aqueous solution via nasogastric tube. Dose of 0.5 to 2 mg/kg every six hours.

Outcomes/endpoints:
Serum theophylline concentrations two hours after midday dose and two,four, six, eight, 11,14, and 24 hour after cessation of therapy. Full absorption assumed.
Statistical Methods
Descriptive statistics.

Results
Recruitment/ Number analysed
Recruitement not addressed. Data from eight infants analysed.

Baseline data
Five males and three females. Gestational week 26-29. Birth weight 887 – 1480 g).

Efficacy results
T½ 12-29 hours. Vd 0.71-2.86 L/kg. Clearance mean 39 ml/hr/kg (range 23-68).

Safety results
A dose of 2 mg/kg every six hours in all infants except one, resulted in variable serum concentrations often exceeding the therapeutic range of 6 to 11 mg/l.

Conclusion
Clearance is lower and half life therefore considerable longer in newborn infants compared to older children. Vd also larger, and the authors discuss that this may be due to a larger fraction of body water and diminished binding to plasma proteins.
Data consistent with finding by Aranda et al (2).

Assessor's comments:
A small, but valuable study of the pharmacokinetics of oral theophylline in premature neonates. Clearance low in preterm neonates.

Islam SI et al. 2004 (29)
Title: *Pharmacokinetics of theophylline in preterm neonates during the first month of life.*

Description
A pharmacokinetic study of iv. theophyllin in 50 preterm neonates including coadministration of phenabarbiturates (inducer) and cimetidine (inhibitor) in some of the patients due to convulsions and gastrointestinal bleeding respectively.

Methods
Objective(s)
To estimate the theophylline pharmacokinetic parameters in preterm neonates with apnea during the first month of life in order to optimize its dosage regimen.

Study design
Descriptive study

Study population /Sample size
Fifty preterm (<34 weeks GA) neonates in Saudia Arabia treated with theophylline within the first month of life for apnea of prematurity.

Treatments
Theophylline was given in the form of aminophylline by slow intravenous (IV) over 10 minutes. Loading dose (LD) of 3-6 mg/kg was given followed by a maintenance dose (MD) of 0.5-3 mg/kg/12 hours. For the management of convulsion (8 patients), 20 mg/kg of phenobarbital was given IV then followed by 5mg/kg/day. For management of gastrointestinal bleeding (19 patients) cimetidine was given IV in a dose of 5mg/kg/12 hours.

Outcomes/endpoints
Serum theophylline concentration was measured one hour post loading dose, and the second on the sixth day halfway between doses (steady state concentration).

Statistical Methods
Pharmacokinetic (PK) analysis was performed using conventional PK equations. Analysis of variance was used to determine significant differences between means. Chi Square was used for comparison of ratios. Regression analysis was used to investigate correlation between demographic variables and PKP.

Results
Recruitment/ Number analysed
Fifty patients recruited. Eight received phenobarbiturates and were excluded from the pharmacokinetic analyses.

Baseline data
Males/females: 28/22.
Patient in PK analyses (n=42): Males/females: 25/17. Ethnic origin: 8 african and 34 asian. GA Mean (SD) 30.2 (1.60) weeks, range 27-33. Birth weigth mean (SD) 1.34 (0.26)kg, range 0.88-2.3.

Efficacy results
Patients that received phenobarbital showed significantly lower mean T½ and significantly higher mean clearance than the other patients. Cimetidine did not
Vd mean (SD) 0.77 (0.25)L/kg. Clearance mean (SD) 0.019 (0.006) L/kg/h. T½ mean (SD) 30. 7 (12.1). High interintervidual variability.

Safety results
Thirty-six percent of samples were within therapeutic range (6-12 ug/ml), 57% were sub-therapeutic, and 7% were potentially toxic.

Conclusion
Poor correlation between pharmacokinetic parameters,gestational age and birth weigth. Altered metabolic pathway of theophylline -mediated through CYP subfamily different from those in children and adults- could explain the observed significant induction of TH metabolism by concomitant administration of phenobarbital in preterm neonates. Metabolism was not significantly affected by cimetidine.
The authors suggest a dosing regimen based on theophylline clearance.

Assessor's comments:
Additionally evidence of clinical significant interaction in preterm neonates between theophylline and phenobarbiturate like in adults and older children, but not between pheophylline and cimetidine. This indicates an altered metabolic pathway for theophylline in preterm neonates. Interaction with Phenobarbital is mentioned in section 4.5.

1.b. Age range 0-16 years

Nassif EG et al. 1981 (45)
Title: ***Theophylline disposition in infancy.***

Description
After having observed seizures and consequently brain damage due to presumably theophylline toxicity the authors conducted an investigation of the dosage requirements and pharmacokinetics of theophylline among infants receiving theophylline continuously or repeatedly for symptoms compatible with asthma.

Methods
Objective(s)
Investigation of the dosage requirements and pharmacokinetics of theophylline among infants.

Study design
Observational study.

Study population /Sample size
Fifty infants, 6-48 weeks of age.

Treatments
Oral theophylline. Either a liquid formulation (Slo-phyllin-GG) or sustained release preparation (Slo-phyllin Gyrocaps) was used in all patients.
Treatment doses were guided by serum concentrations.

Outcomes/endpoints
The mean dose of theophylline required to achieve a therapeutic concentration of 10 to 20 ug/ml. Peak serum theophylline concentrations were obtained from blood drawn two hours after a liquid or four hours after a sustained-release formulation.

Statistical Methods
Relationships between age and disposition were determined by-linear regression using least squares for both age vs. half-life of elimination and age vs dose required to achieve a therapeutic serum concentration.

Results
Recruitment/ Number analysed
Data from the 50 patients were used in the dose study. T½ was determined in 12 of the infants.

Baseline data

Fifty infants (40 boys,10 girls), 6-48 weeks of age.

Efficacy results

Dosage requirements to achieve a therapeutic serum concentration between 10 to 20 ug/ml were variable but on average increased with age. The mean dose among the infants less than 4 months of age was 12.4 mg/kg/day and increased to 22.4 mg/kg/day after 8 months of age.

The relationship between age and dosage requirements can be expressed by the least squares determination of the linear regression: Dose (mg/kg/day) = 8 + 0.3 times age in weeks.

Clearances in four patients between 10 and 20 weeks of age ranged from 0.29 to 0.57 (mean 0.44) ml/kg/minute.

Half-lives of elimination among the infants studied correspondingly decreased with increasing age.

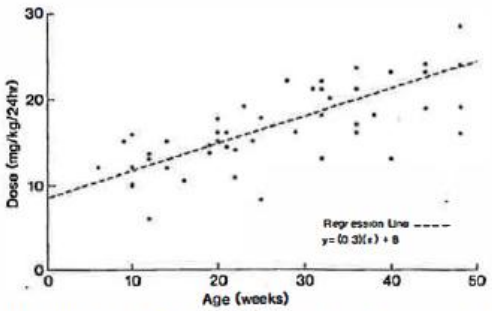


Fig. 1. Relationship between age and dose requirements to attain a serum theophylline concentration of 10 to 20 μg/ml ($r = 0.74$, $P < 0.001$).

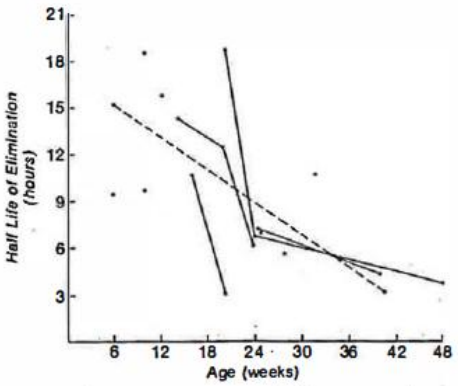


Fig. 2. Relationship of elimination half-life to age. The solid lines connect data points for four patients with serial measurements. The dashed line is the least squares regression for all of the data points ($r = 0.68$, $P < 0.001$).

Safety results

Considerable inter-patient variability was observed at all ages.

Conclusion

The authors stated that, when continuous treatment with theophylline is appropriate, the risk of adverse effects is minimized when doses initially are no higher than two-thirds the average dose requirements for age, and are increased in approximately 25% increments to mean age-adjusted dosage.

Serum theophylline concentrations should be measured to guide final dosage.

Assessor's comments:

Theophylline dose requirement increases with age in the first year of life.

Treatment of infants with theophylline is as safe as for older children if the immature and developing pharmacokinetics are taken into account, hence dose adjusted to the prolonged half live.

Rosen JP et al. 1979 (55)
Title: *Theophylline pharmacokinetics in the young infant.*

Description
Pharmacokinetic study of 13 infants treated with a single dose of theophylline.

Methods
Objective(s)
To investigate the pharmacokinetics of theophylline in infants.

Study design
Pharmacokinetic study.

Study population /Sample size
Thirteen infants (4 to 18 months), who were not acutely ill, but with recurrent pulmonary symptoms. All patients were on a maintenance regimen of daily anhydrous theophylline prior to the study.

Treatments
Twelve patients were given an oral dose of 5 mg/kg as a 20% alcoholic solution followed by 4 oz of water. One patient received a intravenously dose because of recurrent aspirations.

Outcomes/endpoints
Blood samples to measure serum theophylline, drawn at zero, one half, one, two, three, four, six, and eight hours after dose administration.

Statistical Methods
The data were fitted to a first order one-compartment pharmacokinetic model using linear regression analysis. Assumed bioavailability = 100%

Results
Recruitment/ Number analysed
Thirteen infants admitted to the Clinical Research Center for study.

Baseline data
Age 4 – 18 months. No information regarding sex. Three patients with other medication (Ferrous sulphate, Phenobarbital, metaproterenol respectively).

Efficacy results
T½ mean was 4.8 ± 1.5 hours range 2.5-7.9 hours.
There was an inverse correlation between T½ and age over the entire range.
Mean Vd was 0.56 ± 0.14 liter/kg range 0.38-0.83 liter/kg.
Mean body clearance was 0.089 ± 0.031 liter/kg/hr range 0.046-0.156 liter/kg/hr.

Safety results
Infants aged 4, 4½ and 5 months had a T½ substantially longer than those infants > 5 months.

Conclusion

Data reveal that infants can achieve childhood clearance rates of elimination by 6 months of age.
In infants less than 6 months of age, the authors reaffirm individualization of theophylline dosage to maintain therapeutic levels and avoid toxicity.

Assessor's comments:
Valuable study of the pharmacokinetics in infants. Childhood clearance rate achieved by 6 months of age. This already mentioned in SmPCs.

Vanto T et al. 1989 (65)
Title: *Efficacy and pharmacokinetics of slow release theophylline in preschool children with intermittent episodes of asthma.*

Description
Randomized, placebo controlled study evaluating the efficacy of theophylline in preschool children with intermittent episodes of asthma.

Methods
Objective(s)
to evaluate the clinical efficacy of theophylline in asthmatic children, ages 1 to 3 years, and to investigate the kinetics of theophylline in these patients

Study design
Randomized, placebo controlled study. During a run-in period the patients were given increasing doses of theophylline until steady state. After the run-in period the patients were randomly divided into two groups: continuing titrated dose of theophylline or placebo I three months.

Study population /Sample size
Fourty-six out-patients with three or more attacks of asthma during the twelve months prior to the study, and who had had at least one attack necessitating hospitalization.

Treatments
During a run-in period the patients were given increasing doses of theophylline (Theo-Dur Sprinkle1li, AB Draco, Lund, Sweden). The initial dose was between 10 and 18 mg/kg/day and the upper limit was 35 mg/kg/day. The intended goal for the pre-dose morning serum level was 7.5-12.0 mg/l at the end of the run-in period.

Outcomes/endpoints
Parents scored symptoms of dyspnea, cough, and wheeze during the day and night on a diary card with a 3 grade scale (0, no symptoms; 1 , some symptoms; 2, troublesome symptoms).

Statistical Methods
The clinical efficacy of the two treatments was analyzed by comparing the means of the clinical symptom scores from the two treatment periods.

Results
Recruitment/ Number analysed

Fourty-six recruited. Nine excluded due to too high or low theophylline concentrations. Three patients withdrawn in the run-in period (two because of possible adverse symptoms, one because of improvement of symptoms).
Thirty-four patients were included in the final evaluation, 16 in the control group and 18 receiving theophylline in a daily dose of 21.2±0.9 mg/kg.

Baseline data
16 females and 30 males, with a mean age of 1.7 years (range 1 to 3 years

Efficacy results
The daily symptom score was 0.l7±0.l8 in the theophylline group and 0.10±0.09 in the control group (no significant difference; NS).
The consumption of terbutaline elixir during the study period was 549±88 ml in the theophylline group and 338±71 ml in the control group (NS).
No difference was observed between the placebo group and the theophylline group in the use of additional medication or in the frequency of severe wheezing attacks.

Safety results
Three children were withdrawn from the study during the run-in period: two of them because of possible adverse symptoms.
Twenty-four patients showed a non-linear kinetic during the run-in period. A step by step increase in the dose resulted in a steep increase in serum concentration at a dose of around 20 mg/kg/day in most children.

Conclusion
The data show no specific benefit from the maintenance therapy with theophylline in young preschool children with intermittent episodes of asthma.
If theophylline is used in this age group, careful monitoring of the serum level is necessary after each dose increment, since the kinetics of theophylline is non-linear in this age group.

Assessor's comments:
Theophylline used on a long-term basis is not generally effective in preventing episodes of asthma in young children age 1 – 3 years. Additionally, careful monitoring of the serum level is necessary after each dose increment, since the kinetics of theophylline is non-linear in this age group.

Loughnan PM et al. 1976 (39)
Title: *Pharmacokinetic analysis of the disposition of intravenous theophylline in young children.*

Description
An investigation of the disposition of theophylline in children, and a comparison with an adult historic control. The authors also calculated predictive maintenance dose and loading dose based on pharmacokinetic parameters.

Methods
Objective(s)

To investigate the disposition of theophylline in children and compare it with an adult historic control and calculate predictive maintenance dose and loading dose based on pharmacokinetic parameters.

Study design
Pharmacokinetic analysis of the disposition of intravenous theophylline in young children and a comparison with historic data from adults.

Study population /Sample size
Ten asthmatic children.

Treatments
A single intravenous dose of theophylline, 3.2 mg/kg

Outcomes/endpoints
Serum theophylline was measured 0, 5, 10, 15, 25, 40, 60, and 120 minutes, then at two hourly intervals until eight hours after the injection.

Statistical Methods
The plasma concentration-time curves for individual patients were subjected to analysis utilizing a nonlinear, least squares curve-fitting program.

Results
Recruitment/ Number analysed
Ten patients with more severe and chronic asthma were selected from the allergy clinic.

Baseline data
Age mean (SD) 2.5 (0.9) range 1.3 – 4.4, 50 % males. Weight mean (SD) 12.5 (2.1). All of the patients treated with various com-medication including phenobarbital, prednisolone and/or ephidrine.

Efficacy results
The mean plasma theophylline clearance was 0.100 ± 0.036 l/kg/hr, T½ 3.38 ± 1.11 hr and Vd 0.25 ± 0.13 l/kg.
The one- and two-compartment analyses yield almost identical maintenance and loading doses of aminophylline. The use of a one-compartment model in the calculation of therapeutic regimens for theophylline in young children is therefore acceptable.

Safety results
Plasma theophylline clearance was approximately 40% greater in these children than that reported in adults, mainly due to an increased rate of drug elimination.
Large inter-individual differences yielded almost identical dosage regimens designed to rapidly achieve and maintain a chosen plasma theophylline concentration.
theophylline concentration.

Conclusion
The authors suggest, based on their findings, a loading dose of 5.6 mg/kg followed by a maintenance dose of 30 mg/kg/day would be appropriate to achieve and maintain a mean steady state plasma concentration of theophylline of 10 ug/ml, though potential toxicity of that maintenance dose rate was not excluded.

Assessor's comments:

Small study. Substantial co-medication, including phenobarbital that potentially will increase theophylline metabolism. Indication of increased rate of elimination in children compared to adults. One-compartment model acceptable in therapeutic doses.

Vaughan LM et al. 1988. (66)
Title: ***Oral bioavailability of slow-release theophylline from unencapsulated beads in preschool children with chronic asthma.***

Description
An examination of the relative bioavailability of Slo-bid Gyrocaps and Theo-Dur Sprinkle in a preschool population using an older formulation with more rapid absorption given every eight hours as a reference.

Methods
Objective(s)
To examine the potential for reliably complete absorption of two different slow release formulations in young children compared to an older formulation with more rapid absorption.

Study design
Two separate crossover multiple-dose trials.

Study population /Sample size
Thirteen preschool children requiring maintenance theophylline for control of chronic asthma.

Treatments
Seven received Slo-bid and seven received Theo-Dur Sprinkle and the same 12-h dosing schedule was used for each. Because of earlier product availability, the Theo-Dur Sprinkle study was begun first and random assignment was therefore not performed. All received Slo-PhyIlin Gyrocaps every 8 h as the reference formulation. Dosage of the test drug was initially similar to that determined for the Gyrocaps. The morning dose of medication on the day of sampling was given shortly before breakfast and the evening dose -2 h after supper.

Outcomes/endpoints
To minimize invasiveness of sampling in these young children, theophylline was measured in saliva. Silava samples were collected hourly for one dosing interval, and 4-hourly for the remainder of each 24-h study period.

Statistical Methods
Relative bioavailability was calculated by comparing the 24-h area under the salivary stick concentration-time curves (AUC) after normalizing for dosage differences. Paired t tests were used to compare dose-normalized AUCs with that obtained with the Slo-Phyllin Gyrocap reference**.**

Results
Recruitment/ Number analysed
Thirteen patients. One patient participated in both trials, resulting in seven patients for each trial.

Baseline data
Theo-Dur group: Age mean (SEM) 3 (0.5) years, range 1-5 years. 4 males, 3 females
Slo-bid group: Age mean (SEM) 4.5 (0.5) years, range 3-7 years. 4 males, 3 females.

Efficacy results
The mean ± SEM bioavailability of Theo-Dur Sprinkle relative to the Slo-Phyllin Gyrocap reference based on the dose adjusted AUCs was 66 ± 8%, with five of seven subjects below 75%, whereas the relative bioavailability of Slo-bid was 109 ± 5%, with no subjects below 93%.

Safety results
Risk of toxicity if formulations are substituted.

Conclusion
Substitution of more completely absorbed formulations can then inadvertently result in substantially higher serum concentrations.
The availability of theophylline formulations with incomplete absorption presents a potential hazard of theophylline treatment

Assessor's comments:
Differences in AUC between rapid and slow release preparation. Emphasize the need for measure of serum theophylline levels in the case of swift between formulations. This already mentioned in section 4.2.Theophylline concentrations measured in saliva, not plasma. Saliva and blood correlation validated in another study. Saliva theophylline concentrations instead of blood would decrease the need for blood samples.
It is noted in section 4.2 in the SPC for Theo-DUR that plasma concentration should be measured if patients shift between theophylline products.

Zaske DE et al. 1977 (73)
Title: ***Oral aminophylline therapy. Increased dosage requirements in children***

Description
A description of the age-dependent pharmacokinetics of oral aminophylline and the drug's oral dosage requirements in different age groups.

Methods
Objective(s)
To describe the age-dependent pharmacokinetics of oral aminophylline and the drug's oral dosage requirements in different age groups.

Study design
Dose-concentration correlation study.

Study population /Sample size
59 children and 114 adults. The children were receiving aminophylline as therapy for bronchial asthma and the adults for chronic obstructive lung disease.

Treatments
Uncoated tablets of aminophylline

Outcomes/endpoints
An estimate of theophylline elimination was obtained by dividing the daily oral aminophylline dose by the trough serum theophylline concentration.

Statistical Methods
Unpaired T-tests

Results
Recruitment/ Number analysed
59 children and 114 adults.

Baseline data
The children age ranged between 1 to 18 years with a mean age of 9.9 years. The adults' ages ranged between 20 to 85 years with a mean age of 54 years.

Efficacy results
The mean apparent theophylline clearance (ATC) determined in 59 children was significantly higher ($P < .001$) than determined in 114 adults (84.8 versus 51.4 ml/hr/kg). The younger children (1 to 9 years) eliminated theophylline more rapidly than the older children (10 to 18 years) (93.8 versus 77.3 ml/hr/kg).

Safety results
The use of these higher dosages did not result in any observed increase in side effects when the serum levels were maintained in the therapeutic range. Because of the large variation in theophylline elimination in both adults and children, serum concentrations should be determined several days after initiating therapy and after a dosage adjustment has been made.

Conclusion
Larger doses (mg/kg) of aminophylline were necessary for children than for adults to achieve similar therapeutic serum concentrations.
The guidelines for aminophylline were 28.0, 23.2, and 15.6 mg/kg/day administered in four divided doses for the younger children, older children, and adults, respectively. Monitoring of serum levels is suggested to further individualize the patient's aminophylline therapy.

Assessor's comments:
The study shows that elimination is more rapid in children, and that children therefore require larger doses.

Asmus MJ et al. 1997. (3)
Title: ***Apparent decrease in population clearance of theophylline: implications for dosage.***

Description
Dose requirements of theophylline in 1990-1995 compared to 1978-1983.

Methods
Objective(s)

To investigate an apparent increase in dosage requirements to attain peak serum concentrations of 10 to 20 ug/ml.

Study design
Observational study of therapeutic drug monitoring data. Dosage requirements in cohort from 1990 – 1995 compared to cohort from 1978 – 1983.

Study population /Sample size
Patients with chronic asthma treated with theophylline by the Pediatric Allergy and Pulmonary Clinic at the University of Iowa from 1990 to 1994 (n = 300) and at the pediatric Pulmonary Clinic at the University of Florida from 1992 to 1995 (n = 93).

Treatments
All patients were receiving a reliably absorbed slow-release theophylline product

Outcomes/endpoints
Dosage requirements needed to attain peak serum concentrations of 10 to 20 ug/ml.

Statistical Methods
Single-factor ANOVA and the Tukey multiple comparison test.

Results
Recruitment/ Number analysed
There were 393 patients in the first cohort (1990-1995). The number of patients in the other cohort (1978-1983) is unclear.

Baseline data
Not addressed.

Efficacy results
Mean theophylline dosage requirements during the period of this study were 17 mg/kg/day in patients from 1 to 8.9 years old (n = 134 patients), 15 mg/kg/day in patients from 9 to 11.9 years old (n = 75 patients), 13 mg/kg/day in patients from 12 to 15.9 years old (n = 86 patients), and 1 1 mg/kg/day in 98 patients >16 years old (Fig. 1). These results were approximately 25% lower among all age groups compared with those observed previously from 1978 to 1983 ($p < 0.001$).
Mean serum concentrations during both time periods were similar.

Safety results
The authors argue that guidelines for theophylline dosage need to be revised based on their data.

Conclusion
The data confirm the author's impression that theophylline dosage requirements needed to attain serum concentrations between 10 and 20 ug/ml are currently lower than those determined in an identical manner 12 to 18 years ago, and guidelines therefore should be revised.
The authors speculate whether it is this change in exposure to environmental tobacco smoke that has decreased theophylline clearance and consequently theophylline dose requirements in the population.

Assessor's comments:

Apparently there is a 25 % fall in the average required dosage of theophylline in 1990-1995 compared to 1978-1983 to attain recommended serum concentration. It is an observational study and the result might be contributed to confounding factors, including change in prescription patterns, co-morbidity etc.
Reason for change? Change in environmental tobacco exposure?

Tateishi T et al. 1999 (63)
Title: *Developmental changes in urinary elimination of theophylline and its metabolites in pediatric patients*

Description
An investigation of the developmental changes in the pattern of urinary metabolites of theophylline, a substrate for CYPIA2, to study when CYPIA2, which is absent in the perinatal period fully develops during childhood.

Methods
Objective(s)
To determine whenCYPIA2 activity is fully developed.

Study design
The patients were given a constant infusion of theophylline. Three urinary samples and one blood sample was collected in steady state. The urinary ratio of the metabolites 3MX or IMU to theophylline can be considered as a measure of *in vivo* CYPIA2 activity.

Study population /Sample size
Fifty-one pediatric patients undergoing treatment for neonatal apnea (11 = 7) and bronchial asthma (11 = 44) were enrolled in the study.

Treatments
Doses of intravenous aminophylline of 2-4 mg/kg/day or 15-20 mg/kg/day were administered to patients less than or more than 1 year of age respectively.

Outcomes/endpoints
Plasma theophylline concentration. Urinary concentrations of theophylline and its metabolites: I-methyluric acid (l MU), 3-methylxanthine (3MX), and 1,3-dimethyluric acid (DMU).

Statistical Methods
Data are presented as mean ± SD. Statistical significance was determined by using one-way analysis of variance with Fisher's protected least significant difference test for post hoc comparisons.

Results
Recruitment/ Number analysed
Fifty-one pediatric patients: Three urinary samples and one blood sample was collected from each patient.

Baseline data
Ten patients were less than one year of age; seven patients were between 1 and 3 years; 9 were between 3 and 5 years old; 15 were between 5 and 10 years and 10 were between 10 and 15 years. Females/males: 28/23.

Efficacy results
The mean ratio of 3MX or IMU to theophylline in patients over 3 y of age was significantly higher than that in those under 3 y of age.

Safety results
The ratios gradually increased by approximately 3 y of age. In patients over 3 y of age, the ratios showed a marked inter-individual variation and higher mean values compared with those under 3 y of age. The huge scatter of the ratios implies a wide inter-individual variation of theophylline metabolism and probably in vivo CYPIA2 activity.

Conclusion
The findings of the present study suggest that CYPIA2 activity may be programmed to mature by around 3 years of age.

Assessor's comments:
Theophylline is a substrate of CYP1A2. The activity of CYP1A2 is not fully developed until the age of 3. This may have implications for the dosage in small children, as well as other drugs metabolized by CYP1A2.

Kizu J et al. 1999 (34)
Title: *Enhanced theophylline metabolism in patients with bronchial asthma at age 4 and under*

Description
The plasma levels of theophylline (TP) and its metabolites were measured in patients with bronchial asthma who were treated with a slow-release preparation of TP.

Methods
Objective(s)
To examine theophylline metabolism in plasma samples from patients of a wide range of ages receiving round-the-clock therapy with slow release preparation of theophyline, including infants.

Study design
Plasma samples and measurement of metabolites in relation to theophylline concentration from patients treated with slow release preparation of theophyline.

Study population /Sample size
Eighty-four plasma samples collected from 46 out-patients and in-patients with bronchial asthma.

Treatments
The mean doses of TP administered were 18.5 mg/kg/day for patients aged 1–4 years (*n* = 25, average body weight 15.1 kg), 15.5 mg/kg/day for those aged 5–12 years (*n* = 21, average 26.0 kg), and 12.3 mg/kg/day for those aged 13–55 years (*n* = 18, average 52.0 kg).

Outcomes/endpoints
Correlation coefficients of plasma metabolites and theophylline.

Statistical Methods
Fisher transformation (difference between correlation coefficients)

Results
Recruitment/ Number analysed
Eighty-four plasma samples collected from 46 out-patients and in-patients with bronchial asthma.

Baseline data
27 males and 19 females, aged 1–55 years, 1–4 years (*n* = 25, average body weight 15.1 kg), 5–12 years (*n* = 21, average 26.0 kg), and 13–55 years (*n* = 18, average 52.0 kg).

Efficacy results
The plasma TP levels were lower in younger patients in spite of the administration of higher doses.
The 1MU:TP and 3MX:TP ratios of the 1–4-year-old group were significantly higher than those of the other groups

Safety results

Conclusion
The 1MU:TP and 3MX:TP ratios of the 1–4-year-old group were significantly higher than those of the other groups suggesting enhanced activity of drug-metabolizing enzymes during infancy.

Assessor's comments:
The authors suggest that the drug-metabolizing enzymes have enhanced activity during infancy, in the study in the 1-4-year-old group. This differs from the study by Tateishi (63). The treatment in this study is a slow-release preparation of theophylline. How the drug is administered to the small children is not mentioned.

Welch MJ et al. 1985 (69)
Title: *Steady-state evaluation of twice-a-day dosing of a new sustained-release theophylline preparation for young children*

Description
Evaluation to evaluate if Theo-Dur Sprinkle@ (TS) can be given on a b.i.d. basis with acceptable steady-state theophylline levels in children with asthma.

Methods
Objective(s)
To study the absorption properties of a new sustained-release theophylline, Theo-Dur Sprinkle@ (TS) to see if this formulation, when given on a b.i.d. basis, results in acceptable steady-state theophylline levels in children with chronic asthma.

Study design
Pharmacokinetic study, after multiple TS dosing, had serum theophylline levels determined over a 10-hr period after a morning TS dose.

Study population /Sample size

Twelve patients with asthma (age 5-8years).

Treatments
Patients were initially given b.i.d. TS at a dose of 20-24 mg/kg per day; this dose was then titrated upward based on peak serum theophylline levels in the therapeutic range 10-20ug/ml drawn 4 to 6 hr after morning dosing. Medication was given by mixing it into apple sauce or jelly; children were not allowed to chew the beads.

Outcomes/endpoints
Serum theophylline levels were determined at 2, 4, 8, and 10 hr after the morning dose. An estimate of the percent peak-to-trough fluctuation was determined on each patient by designating the peak and trough theophylline level as the highest and lowest serum levels measured for that patient during the 10-hr study day. The percent peak-to-trough fluctuation was calculated.

Statistical Methods
The mean percentage of peak-to-trough fluctuation.

Results
Recruitment/ Number analysed
Twelve pediatric patients with chronic, moderately severe asthma.

Baseline data
Mean age of 7.4 years (range 5-8 years); eight were boys. TS dose ranging from 21 to 35 mg/kg per day mean=28.5 ± 5.0 (SD) to obtain peak steady-state serum theophylline levels in the therapeutic range.

Efficacy results
The mean percentage of peak-to-trough fluctuation seen in the l2 children was 53% (range 8-100%).

Safety results
All patients accepted the medication well, experienced minimal to no side effects, and had good compliance as based on pill counts. No patients or parents reported beads in the stool.
In one of the patients in this study who required a very high dose of TS only 75% was absorbed under steady-state conditions compared to a rapid-acting liquid theophylline (Elkicon@) and to Theo-Dur tablets.

Conclusion
Fluctuations in serum theophylline concentrations were acceptable. The high doses of TS suggested incomplete absorption of TS.

Assessor's comments:
12.hour dosing appear safe, but the apparent variable absorption emphasizes the need for careful substitution between products.

Kjellman N-IM et al. 1988 (35)
Title: *Theophylline pharmacokinetics in children, comparing sustained release spheres (Theo-Dur sprinkle) with elixir*

Description
A randomized cross over study to compare the steady state fluctuation of theophylline plasma concentrations in children during a 24 h interval after intake of sustained release theophylline beads or a theophylline elixir.

Methods
Objective(s)
The aim of this study was to compare the steady state fluctuation of theophylline plasma concentrations in children during a 24 h interval after intake of Theo-Dur sprinkle (TDS)sustained release theophylline beads or a theophylline elixir and to find out patients' and parents' preference.

Study design
Company-initiated pharmacokinetic study. Open study with a randomized cross over design.

Study population /Sample size
Eight ambulatory children with asthma

Treatments
The individual theophylline dose was about 20 mg/kg body weight per day. The drugs used were TDS capsules 75 and 125 mg (splitting of capsule contents was not allowed) and theophylline elixir. The daily dose of TDS was divided equally into two doses,and the elixir dose into three doses.

Outcomes/endpoints
Cmax and Cmin were identified during the 24-h period. The fluctuations between Cmax and Cmin were determined with the following formula: Fluctuation (%) = ((CmaxCmin)/Cmin) X 100

Statistical Methods
The area under the 0-24 h concentration time curve (AUC) was calculated by the trapezoidal method. The relative bioavailability of theophylline from TDS was calculatedby relating the AUC value to that of the elixir after correcting for the differences in doses.
The mean steady state concentration Css was calculated as AUC (0-24)/24.
Wilcoxon's signed rank test was used in the statistical analysis.

Results
Recruitment/ Number analysed
The number of blood samples drawn was a compromise between ethical and pharmacokinetical demands.

Baseline data
Eight ambulatory children with asthma (1 F + 7 M) were studied. Their mean age was 8 years (range 4-10) and mean weight 26.4 kg (range 17. 5-36.0).

Efficacy results
The mean relative bioavailability of theophylline from TDS was 94% (range 54%-121%)

Safety results

Four patients reported symptoms from the gastrointestinal tract and from CNS. There was no difference either in the frequency or in the duration of side effects between the two treatment periods.

Conclusion
TDS showed satisfactory sustained release properties but the study confirmed the need for individually tailored dosage of theophylline based on monitoring of symptoms and serum concentrations.

Assessor's comments:
Satisfactory sustained release properties and possible b.i.d administration, but again substantial inter-individual variation and need for monitoring of serum concentrations.

Ginchansky E et al 1977 (19)
Title: *Relationship of theophylline clearance to oral dosage in children with chronic asthma*

Description
The study investigates if an oral dosage regimen (6 hourly oral dose) can be predicted based on theophylline clearance.

Methods
Objective(s)
To investigate the clearance of theophylline in children with chronic asthma and its variability in relation to oral dosage.

Study design
Pharmacokinetic study. Calculation of clearance based on infusion until steady state and thereafter determination of oral dosage. In steady state (2 weeks) estimation of peak and trough levels.

Study population /Sample size
Twenty-three children who were receiving theophylline prophylaxis for chronic asthma

Treatments
Theophylline was administered by constant intravenous infusion 0.85 mg/kg/hour until steady state was reached. Afterwards treatment with calculated oral dosage (6-hour dosing interval) in 2 weeks.

Outcomes/endpoints
Relationship between clearance and oral dosage requirements. Estimation of peak and trough levels.

Statistical Methods
Relationship between weight adjusted clearance and age was examined using a Spearman rank correlation coefficient (r,). Relationship between clearance and oral dosage requirements was examined by performing linear regression analysis and determining correlation coefficients for, clearance and standardized responses of serum theophylline concentrations resulting from oral dosages (peak and trough serum theophylline concentrations + 6 hourly oral dosage). The relationship between clearance and peak-trough differentials during chronic oral dosing was similarly examined.

Results

Recruitment/ Number analysed

Twenty-three children who were receiving theophylline prophylaxis for chronic asthma. Sixteen of these patients were available from one to seven months later for repeat infusion of intravenous theophylline at a similar dosage.

Baseline data

Ten girls and 13 boys; ages ranged from four to 15. In addition. Thirteen received a corticosteroid, and one patient received potassium iodide. Two patients were receiving anticonvulsants (methsuximide in one and primidone in the other).

Efficacy results

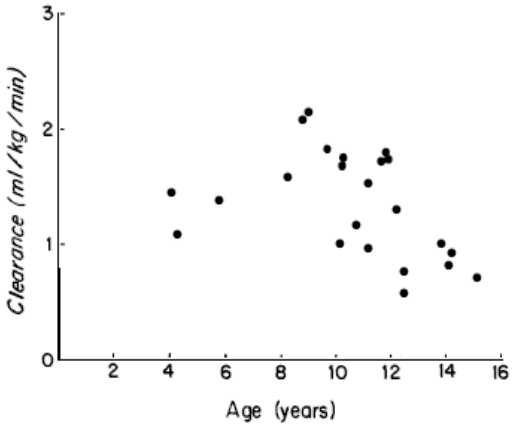


Fig. 1. Relationship of theophylline clearance to age. A significant inverse correlation is present ($r_s = -0.46$, $p < 0.025$).

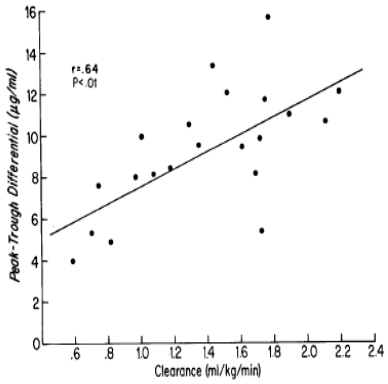


Fig. 3. Relationship between theophylline clearance and peak-trough differentials during chronic oral dosing every 6 hours. The peak-trough differences are the means of duplicate determinations.

Clearance was 1.35 ± 0.46 ml/kg/minute (range - 0.59 to 2.18 ml/kg/minute). Significant inverse correlation was observed between age and theophylline clearance among these children (Fig. 1).

The differences between the peak and the trough estimates averaged 9.2 ± 3 f.Lg/ml. The more rapid rate of elimination associated with higher clearances also appeared to result in greater differences between the peak and trough estimates resulting in a significant correlation between the peak-trough differentials and clearance (Fig. 3). Based on predicted mean serum concentrations of 13.4 ± 2.2 ug/ml, theophylline doses of 3.4 to 9.1 mg/kg every 6 hours resulted in peak and trough serum of 21.3 ± 3.6 and 12.0 ± 2.7 ug/ml, respectively.

Safety results

Nine of the 21 patients had differences greater than 10 ug/ml,-the interval size of the therapeutic range.

Intrapatient variability over an interval up to seven months, however, was acceptably small, suggesting that dosage requirements, once established for an individual, should remain relatively stable under normal conditions

Conclusion

This study confirms the wide range for theophylline clearance in children and the weight adjusted clearance tends to decrease with age. The small intra patient variability in the duplicate estimates for peak and trough serum concentrations supports the relative consistency of theophylline absorption and elimination within the same patient.
Although oral dosage requirements thus relate closely to theophylline clearance, dosage still cannot be predicted reliably from measurement of theophylline clearances, and must be attained by careful clinical titration guided by measurements of serum theophylline.

Assessor's comments:
Dosage cannot be predicted reliably from measurement of theophylline clearances. Clearance decreases with age. Small intra-patient variability.

Witschital K et al. 1998 (71)
Title: *[Pharmacokinetics of theophylline in sustained-release formulation in young asthmatics] German paper with English summary*

Description
Bioequivalence of two different theophylline sustained release preparations.

Methods
Objective(s)
To investigate the pharmacokinetics of two theophylline sustained release preparations.

Study design
Pharmacokinetic study. Open randomised two-way crossover design.

Study population /Sample size
Twenty children with mild to moderate asthma were recruited,one left the study after an unsuccessful blood sample.

Treatments
Individual dosing of 100-300 mg theophylline twice a day. The capsules of the test formulation were opened and administered on a tablespoonful of apple sauce.

Outcomes/endpoints
All relevant parameters for rate (Cmax ss' Cmin ss' Cav ss' plateau time, peak-trough fluctuation, nocturnal excess, tmax ss) and extent of absorption (AVCss) were calculated for both formulations.

Statistical Methods
Not addressed in the summary

Results
Recruitment/ Number analysed
Nineteen completed the study.

Baseline data
Median age 8 (range 6-12). Median weight 31,3 (range 20,9-49,9).

Efficacy results
Mean plasma concentrations were maintained between 5 and 10 ug/ml,

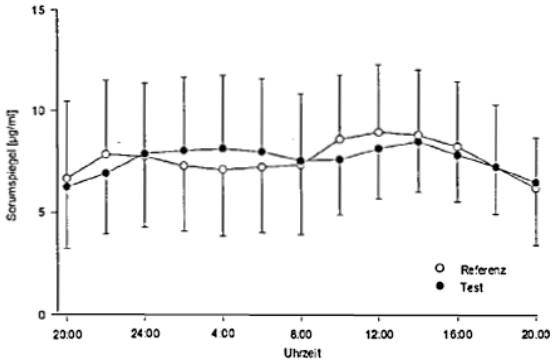


Abb. 1: Theophyllin-Konzentrationen (arith. Mittel ± SA, n = 19) im Serum nach zweimal täglicher Mehrfachdosierung von 200–600 mg/Tag über 6 Tage an jungen weiblichen und männlichen Asthmatikern.

Conclusion
Smooth and predictable concentration/time profiles of both preparations.

Assessor's comments:
Paper in German. Smooth and predictable concentration/time profiles, even though the theophylline capsules were opened and administered on a spoon.

Kato Z et al. 1994 (31)
Title: *Prediction of steady-state serum theophylline concentration in children by first-order and zero-order absorption models*

Methods
Objective(s)
To compare the first-order absorption kinetic model and the zero-order absorption kinetic model for the prediction of serum theophylline concentration to assess the pharmaceutical characteristics of the sustained release formulation, Theo-Dur, in children with asthma.

Study design
Pharmacokinetic study.

Study population /Sample size
Thirteen children with bronchial asthma.

Treatments
Oral dose of TheoDur 200-600 mg/day (8.0-24.0 mg/kg/day) twice daily at 12-hour intervals.

Outcomes/endpoints
Pharmacokinetic parameters: Vd, CL, AR, Ka. Pharmacokinetic parameters for each patient were estimated by a one-compartment open model and fitted to a zero-order or first-order absorption and first-order elimination rate constants.

Statistical Methods
Pharmacokinetic parameters for each patient were estimated by a one-compartment open model with first order or zero-order absorption and first-order elimination ate constants [Imaeda et al. 1988]. Pharmacokinetic parameters for each patient were

estimated on each absorption model using a nonlinear least squares method program,"MULTI".
The precision of the prediction was evaluated by the determination of the An Information Criterion (AIC)

Results
Recruitment/ Number analysed/Baseline data
Thirteen children with bronchial asthma, 9 boys and 4 girls, age 5-14 years old, (mean 9.5 ± 2.6 years) and body weight 18.±5.0 kg (mean 28.3 ± 3.8 kg).

Efficacy results
The regression curve predicted using the zero-order model fitted well to the observed value. In contrast, the use of the first-order model overestimated considerably in the absorption phase.

Safety results

Conclusion
The zero-order absorption kinetic model gave better estimated pharmacokinetic parameters when applied to Theo-Dur than did the first-order absorption kinetic model.

Assessor's comments:
Absorption of sustained release preparations follows zero-order kinetics in children as well as in adults.

Boner AL et al 1987 (9)
Title: ***Absolute and relative bioavailability of a slow release theophylline preparation in asthmatic children***

Description
Bioavailability of sustained release preparation.

Methods
Objective(s)
To describe the pharmacokinetic characteristics and absolute bioavailability
Of a 'once-a-day' theophylline preparation (Teonova®)

Study design
Pharmacokinetic study of absorption and bioavailability in a cross over design.

Study population /Sample size
14 children with chronic asthma, as defined by the American Thoracic Society,' admitted to a residential house for asthmatic children because of frequent admissions to local hospitals due to asthma and because of their poor compliance with therapy..

Treatments
Three theophylline preparations were administered once in a crossover design with a I-week interval between them. a) Aminophylline by intravenous administration; (b) Lysine theophyllinate as an oral solution (40 mg anhydrous theophylline per 1 ml of carrier solution); (c) The slow release preparation of theophylline.
In each case the total dosage given to each child was 100 mg theophylline.

Outcomes/endpoints
Plasma theophylline concentrations at 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 16, 20, 24 and 28 h after administration. mean absorption time (MAT) after oral administration. Absolute (Fa) and relative (Fr) bioavailabilities.

Statistical Methods
The data [weighted (l/observed concentration) were fitted using the non-linear regression analysis program Nonlin. The area under the concentration-time curve (AUC ∞) and the area under the first moment of the concentration-time curve (AUMC∞)were calculated according to the mixed linear-logarithmic trapezoidal rule with extrapolation to infinity.

Results
Recruitment/ Number analysed/Baseline data
Fourteen children, (nine males, five females) aged 7-13 years (mean, 10.9)

Efficacy results
Compared to the orally administered normal release preparation the peak plasma concentration was lower and the time taken to reach this was significantly increased. The mean relative bioavailability of slow release theophylline compared with the normal release oral solution was 83.14 ± 14.69%.

Safety results
One patient had a mean absolute bioavailability of < 60% and four patients had an absolute bioavailability < 80%.

Conclusion
Data indicate that the slow release theophylline preparation studied has characteristic slow release pharmacokinetics. The authors recommend additional studies on asthmatic children to evaluate whether once or twice daily administration allows therapeutic concentrations to be maintained without excessive fluctuations in serum levels.

Assessor's comments:
Low dose and correspondingly low plasma theophylline concentrations < 5 ug/ml. Substantial inter individual variation in bioavailability.

Smolensky MH et al. 1987 (60)
Title: *Administration-time-dependency of the pharmacokinetic behavior and therapeutic effect of a once-a-day theophylline in asthmatic children*

Description
A study of the pharmacokinetic and pharmacodynamic features of once-a-day theophylline when given to school-age patients in the morning,afternoon or evening.

Methods
Objective(s)
To evaluate if the pharmacokinetics and pharmacodynamics of a once-a-day theophylline preparation varies with dosing time.

Study design

Double-blind, placebo-control, crossover study. Randomized for the sequence of treatments.

Study population /Sample size
Eight children with mild to moderate asthma. ,

Treatments
Theophylline dosing at 0600, 1500 or 2100 hr or placebo each of the 4 treatments was given for 7 days during a different week of the study. The total daily dose of theophylline was matched to maintain therapeutic serum theophylline concentration (STC) between 10-20 ug/ml.

Outcomes/endpoints
Blood samples were obtained at 3-hr intervals during the 24hr of each treatment regimen.
Pulmonary function studies were carried out every 3 hr.

Statistical Methods
Data were evaluated by 3-way ANOVA. The serum theophylline data were evaluated for their pharmacokinetic parameters using an approach characterizing once-a day formulations. The means of each parameter were evaluated for statistically significant differences using a 2-way ANOVA.
The Student-Newman-Keuls test was used to determine statistically significant differences between means.

Results
Recruitment/ Number analysed
Children between the ages of 6-17 years meeting the following criteria were recruited into the investigation. Eleven children completed all phases of the investigation, but the report pertains to the findings of only the 8 children, with the explanation than only those, whose data, at the time of this writing, were validated for accuracy, were included.
During the conduct of the investigation, three subjects were dismissed for their inability to successfully complete a second evaluation. Another subject was then recruited.

Baseline data
Age 8-15 years. Males 50 %.

Efficacy results
In comparison to dosing at 0600 hr dosing at 1500 or 2100 hr resulted in greater Cmax, AUCss, Cav**,** and Tmax. Less fluctuation in theophylline concentration for the 0600 hr than the 2100 hr dosing regimen.
Dosing once daily at 2100 hr, as opposed to 0600 or 1500 hr, was associated with greatest fluctuation in theophylline concentration.
Active treatment irrespective of dosing time resulted effect on the airways compared to placebo. In no case was significant variation observed among the regimen groups.

Safety results

Conclusion
The time of dosing had an impact on the fluctuation characteristics, but no influence on efficacy.

Assessor's comments:
Once-a-day preparation had smaller fluctuation when given in the morning, but no difference in efficacy.

Scott PH et al 1989 (57)
Title: ***Day-night differences in steady-state theophylline pharmacokinetics in asthmatic children***

Description
Potential day-night differences of theophylline absorption and disposition were examined in day-active asthmatic children in a random crossover study.

Methods
Objective(s)
To investigate day-night differences of absorption and disposition in day- active asthmatic children of two sustained release theophylline products.

Study design
Pharmacokinetic study. Random crossover.

Study population /Sample size
Twelve day-active asthmatic children meeting the American Thoracic Society criteria for the diagnosis of asthma.

Treatments
Regimen 1:Somophyllin-CRT capsules (Fisons Corporation) every 12 hr for 7 days.
Regimen 2: TheoDur tablets (Key Pharmaceuticals Inc.) every 12 hr for 7 days.
Regimen **3:** Active sustained-release theophylline (Somophylline-CRT or TheoDur) every 12hr for **4** days; followed by placebo every 12 hr for **3** days.
Each patient's dose was chosen to attain a maximum serum theophylline concentration of 15-20 mg/l.
At the end of the third 24-hr study session a 48-hour intravenous aminophylline infusion was started.

Outcomes/endpoints
Blood samples were obtained in steady state immediately pre-dose and at 1,2, 3, 6, 9 and 12 hr post-dose for two consecutive oral dosing intervals. Clearance ***(CL)*** was calculated from the infusion data, and the mean steady-state concentrations ***(CSS)*** for the day and night periods. For the oral theophylline studies, the area under the serum concentration-time curve ***(AUC)*** of each patient was calculated for each dosing interval (day or night) using the trapezoidal method. Maximum **(Cmax.),** pre-dose **(Cp,,)** and minimum (Cmin) concentrations, and the times post-dose of minimum (rmin) and maximum **(tmax)** concentrations were taken directly from the data.

Statistical Methods
The values were then examined for drug product and time of measurement effects using an analysis of variance model.

Results
Recruitment/ Number analysed
Twelve children.

Baseline data
Age 6-17. Four females, eight males.

Efficacy results
Clearances for the day and night period did not differ significantly (1.43 ±0.34 and 1.46 ±0.35 ml/min/kg, respectively).
The mean ***AUC*** for TheoDur was significantly less than that for Somophyllin-CRT.
Regardless of the dosage form, theophylline was absorbed more completely and more rapidly following the 0700 dose, as evidenced by a greater ***AUC*** and a **tmax** that occurred earlier in the dosing interval.

Safety results

Conclusion
Theophylline clearance was not characterized by a circadian rhythm and that absorption of theophylline from both formulations was more rapid and complete during the day than the night.

Assessor's comments:
Both formulations gave rise to lower serum theophylline concentrations following evening administration, but this was related more to an altered absorption pattern than to altered clearance.
Proposal: Daily dose divided with 1/3 in the morning and 2/3 in the evening.

Kanthawatana S et al 1994 (30)
Title: *Bioequivalence of a generic slow-release theophylline tablet in children*

Description
Theoretically, in children who metabolize theophylline rapidly (median half-life = 3.7 hours) a more rapidly absorbed product will produce higher peak and lower trough concentrations than a product with a slower rate of absorption even if the two products are absorbed to the same extent. The study was therefore conducted to determine whether the differences in rate of absorption between the Sidmak product and Theo-Dur were clinically relevant when taken under relative fasting conditions by children who rapidly metabolize theophylline.

Methods
Objective(s)
To determine whether a generic slow-release theophylline tablet (manufactured by Sidmak Laboratories, Inc.) is therapeutically equivalent to a proprietary theophylline tablet, Theo-Dur, in children.

Study design
Bioequivalence study. Prospective, randomized, double-blind, crossover trial.

Study population /Sample size
Thirty-eight children, 6 to 16 years of age, with asthma. Subjects with rapid metabolism were selected by including only those children who required a theophylline dose at or above the mean for age to achieve peak theophylline concentrations in the range 10 to 20 ug/ml.

Treatments
Individualized doses of Theo-Dur or generic tablet (titrated to peak theophylline concentrations of 15 to 20 ug/ml) every 12 hours for 5 days.

Outcomes/endpoints
Bioequivalence: AUC, Cmax, Cmin, and percentage of serum concentration fluctuation
Therapeutic equivalence: The degree of bronchospasm induced by exercise calculated as the maximum post-exercise decrease in FEV1 expressed as a percentage of the baseline value just before the challenge.

Statistical Methods
A two-tailed, paired t-test was used to determine the statistical significance of the difference in mean values for the maximum postexercise percentage of decrease in FEV1, AUC, Cmax, Cmin, and percentage of serum concentration fluctuation.

Results
Recruitment/ Number analysed
Forty-four subjects (21 % of those screened) met all of the entrance criteria and were enrolled and randomly assigned to the study groups; complete exercise data were available for analysis in 37 subjects and complete pharmacokinetic data in 38 subjects (31 male subjects). Seven subjects did not complete the study after randomization.

Baseline data
Age 6 to 16 years. All subjects had a baseline forced expiratory volume in I second more than 80% predicted, and a decrease in FEV 1 of 15% or more after a standard exercise challenge while receiving theophylline doses producing serum concentrations< 1O ug/ml.

Efficacy results
Pharmacodynamics: Neither of the two products effectively inhibited exercised induced bronchospasm.
Pharmacokinetics. There were no significant differences between the mean serum concentration-time curves of the two products.

Safety results
Conclusion
The generic formulation and Theo-Dur were bioequivalent in children.

Assessor's comments:
Bioequivalence between the formulations. Most noteworthy is the low efficacy of both products to inhibit exercised induced bronchospasm.

1.c. Review article

Ogilvie RI et al. 1978 (49)
Title: *Clinical pharmacokinetics of theophylline*

The authors note that the elimination of theophylline is markedly decreased in premature infants, presumably due to a developmentally deficient hepatic cytochrome activity responsible for N-demethylation of theophylline. Clearance is increased in childhood to values above those observed in adult subjects. The rapid clearance in childhood

decreases toward adult values in the late teens. Dose guidelines are approximations only and the wide variability in theophylline clearance between individuals and with disease makes their indiscriminant application hazardous. It is rational to begin with smaller than recommended doses and increase at intervals as tolerated until the recommended amounts are administered.

Assessor's comments:
Though the review is old it reflects and sum up valuable knowledge of the pharmacokinetics and posology of theophylline.

2. Clinical studies in children

Company sponsored clinical study

AWB-BL /UNI-300-400/151092
A single clinical study was included in the Phase I paediatric line listing submissions. Patients aged 5 to 90 years were eligible for inclusion. All together 1023 patients were recruited. The information is insufficient of both age distribution and results in the children to draw any conclusions.

Assessor's comments:
The information in the study is insufficient of both age distribution and results in the children to draw any conclusions.

Trials from the published literature

Barry W et al 1989 (4)
Title: *Once or twice daily theophylline in childhood asthma*

Description
Randomized, single-blind, crossover trial to compare once or twice daily theophylline preparation in children.

Methods
Objective(s)
To compare two sustained release theophylline preparations in terms of efficacy, toxicity and compliance.

Study population /Sample size
Fifty-nine children with known asthma. Patients previously intolerant of xanthines were excluded, as were patients on oral steroids. Theophyllines were either already in use, or were indicated clinically because of poor control.

Treatments
Patients were randomly allocated to receive Slophyllin (SP) twice daily followed by Uniphyllin (UP) once daily or UP followed by SP. Treatment was prescribed to give a total daily dose of theophylline close to 18 mg/kg/day. Dosage was adjusted if necessary to obtain blood levels of 8-20 ug/ml.

Outcomes/endpoints
Symptom scores, beta-agonist usage, compliance by pill counts, evening peak flow rates and maximal expiratory flow-volume.

Statistical Methods
Diary card scores, mean day and night peak flow rates and bronchodilator usage were compared using non-parametric (Wilcoxon signed rank), and parametric tests (t-tests).

Results
Recruitment/ Number analysed
Fifty nine were recruited, Thirty-six patients completed the study. Eight were non-compliant, seven defaulted and eight withdrew because of theophylline related side effects (seven on UP).

Baseline data
Twenty girls and 39 boys, aged 7-14 years, mean(SD)= 10.2(2.2). Before entering the study 19 were taking beta agonists alone, 15 beta agonists and theophylline, nine inhaled steroids and beta-agonists, and 16 inhaled steroids, theophylline and beta-agonists.

Efficacy results
Symptom scores, beta-agonist usage, compliance by pill counts, evening peak flow rates and maximal expiratory flow-volume curves were similar on both treatments. Blood levels of theophylline at 11 am and morning peak flow rates were significantly higher on UP.

Safety results
The once daily preparation was associated with an increased frequency of severe side effects.

Conclusion
Once daily may be more helpful for patients with early morning symptoms, but was associated with an increased frequency of severe side effects.

Assessor's comments:
Large dropout rate due to theophylline related side effects in the once daily treatment group. Trend of improved morning peak flow with the once daily preparation. Once daily administration did not improve compliance in children.

Virchow JC, 1992. (67)
Title: *A prospective trial using salivary-theophylline levels to guide asthma therapy*

Description
Three prospectively studies designed to evaluate the association between theophylline concentration measured in saliva and serum in children.

Methods
Objective(s)
To establish the relationship between theophylline concentration measured in saliva and serum in children.

Study design
Part 1: Samples of saliva and serum collected in 86 children before morning dose.
Each child had received between 100 and 500 mg slow-release theophylline twice daily for at least 7 days (in steady state).
Part 2: In 16 children aged 5 to 13 years (mean, 9.00 ± 2.45 SD) saliva-theophylline levels were measured over a period of 24 hr.
Each child received oral theophylline twice daily.
Part 3: In 50 children theophylline were dosed based on saliva concentrations. As soon as saliva theophylline levels reached a concentration > 5.8 mg/L serum and saliva samples were collected simultaneously.

Outcomes/endpoints
Correlation and regression constants.

Statistical Methods
Pearson's linear regression.

Results
Efficacy results
Part 1: Saliva-theophylline levels between 4.9 and 10.5 mg/L had a sensitivity of 100% in predicting therapeutic serum levels. The specificity, due to 5 false positive predictions, was 91%.

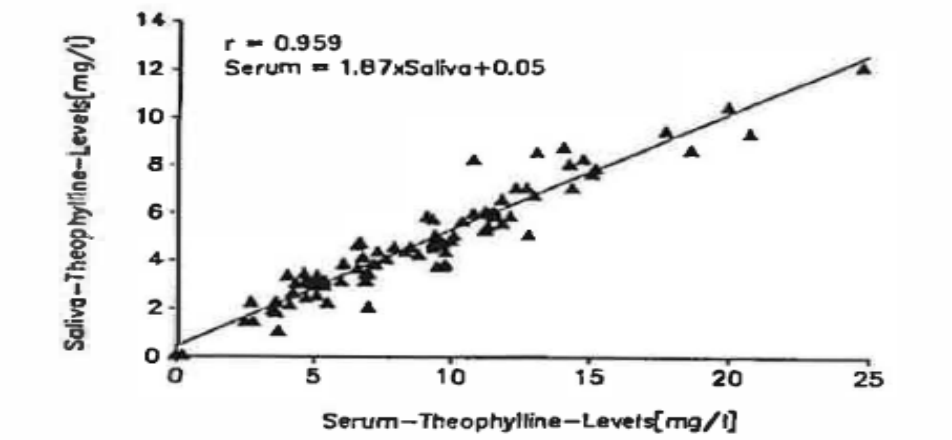


Fig. 2. Correlation between serum- and saliva-theophylline levels and regression equation derived from simultaneously collected serum and saliva samples of 86 theophylline-treated asthmatic children under steady state conditions. *r*, correlation coefficient.

Part 2: The correlation coefficient was between 0.949 and 0.914
Part 3: The upper limit for "therapeutic" saliva-theophylline levels as calculated from the regression equation of the first part of the study was 10.7 mg/L.

Safety results
There were no potentially toxic serum levels that were not reflected by increased salivatory levels.

Conclusion
The authors demonstrate how salivary-theophylline levels can be used safely and effectively to adjust theophylline therapy until therapeutic serum-theophylline levels are achieved. The "therapeutic" saliva theophylline level is 5.8 to 10.7 mg/L.

Assessor's comments:
Non-invasive saliva monitoring might be a safe and equally reliable alternative to serum-theophylline monitoring in children. The study demonstrated substantial day to day variability, probably due to changes in absorption.

Henderson-Smart DJ, 2010 (26)
Title: *Caffeine versus theophylline for apnea in preterm infants*

Description
Cochrane review to investigate the effect of Caffeine versus theophylline for apnea in preterm infants.

Methods
Objective(s)
Evaluate the effect of caffeine compared with theophylline treatment on the risk of apnea and use of mechanical ventilation in preterm infants with recurrent apnea.

Study design
Cochrane review of randomized and quasi-randomized trials.

Study population /Sample size
Five trials involving 108 infants.

Treatments
Exp: standard caffeine = loading dose 10 mg/kg, maintenance dose 1.25 mg/kg/12hrs
Control: theophylline = loading dose 6 mg/kg, maintenance dose 2 mg/kg/12hrs

Outcomes/endpoints
Treatment failure rate (less than 50% reduction in apnea/bradycardia)
Adverse effects, indicated by tachycardia or feed intolerance leading to change in dosing, were lower in the caffeine group (summary relative risk 0.17, 95% CI 0.04 to 0.72). This was reported and consistent in three studies.

Statistical Methods
For meta-analysis of categorical outcomes the summary relative risks (RR) and risk differences (RD) and 95% CI were calculated using a fixed effects model. To calculate the number needed to treat (NNT) the risk difference (RD) was used.

Results
Recruitment/ Number analysed
Preterm neonates (born before 34 weeks gestation) requiring treatment for recurrent apnea of prematurity.

Baseline data
Twenty preterm infants (mean gestational age 30 weeks) included after 24 hour recording documented ≥ 3 apneas.

Efficacy results
There was no difference in the failure rate (number of infants with < 50% reduction in apnea) between caffeine and theophylline at one to three and five to seven days. There

were also no significant differences in the weighted mean differences of apnea at day 1-3 and at day 5-7.
There was insufficient data to undergo subgroup analyses of outcomes of different doses of caffeine or theophylline or outcomes of infants born at different gestational ages or birth weights.

Safety results
Side effects, as indicated by tachycardia or feed intolerance leading to change in dosing, were lower in the caffeine group [RR 0.17; 95% CI 0.04, 0.72; risk difference (RD) -0.29; 95% CI -0.47, - 0.10, number needed to treat (NNT) 3.5; 95%CI 2.1, 9.6].

Conclusion
The authors concluded that the effects of caffeine and theophylline for apnea in preterm infants were similar although theophylline was associated with higher rates of toxicity.

Assessor's comments:
Theophylline seems to have more side effects than caffeine when used for apnea in preterm infants. Caffeine is used in clinical practice today

Eslami Z, 2009. (17)
Title: *Theophylline for prevention of kidney dysfunction in neonates with severe asphyxia*

Description
Placebo controlled, double-blind study from Iran of the effect of a single intravenous bolus of theophylline to prevent/ameliorate kidney dysfunction in neonates with severe asphyxia.

Methods
Objective(s)
This study was designed to determine whether theophylline could prevent or ameliorate kidney dysfunction in term neonates with perinatal asphyxia.

Study design
Double-blind placebo-controlled trial. Randomisation based on a random number table.

Study population /Sample size
Thirty-six infants (GA ≥ 37 weeks), birth weight ≥ 2500 g admitted to neonatal intensive care unit with an Apgar score ≤ 3 in the first minute, an Apgar score of ≤ 6 in the fifth minute, base deficit > 15 mEq/L in cord or arterial blood sample, or the need for severe resuscitation.

Treatments
Theophylline group: single intravenous dose of theophylline, 5 mg/kg.
Control group: 2 mL of placebo (10% dextrose solution).
The infusions were administered in the first 5 minutes after NICU admission during the first hour after birth.

Outcomes/endpoints
Acute kidney failure (defined as an increase in serum creatinine level ≥ 0.3 mg/dL or a serum creatinine level > 1.5 mg/dL for at least 2 consecutive days.), GFR, hematuria.

Statistical Methods
Continuous variables were demonstrated as mean ± standard deviation. The chi-square test, Fisher exact test, and the t test were used for comparisons between the two groups.

Results
Recruitment/ Number analysed
Fourty one recruited, 5 excluded.

Baseline data
No baseline data provided. The two groups were not significantly different in terms of birth weight, gestational age, sex, vaginal or cesarean delivery, arterial blood pH, base deficit, inotrope agent, Apgar score in 1 minutes and 5 minute, resuscitation maneuvers and adrenalin.

Efficacy results
Serum creatinine levels were not significantly different between the theophylline and control groups on the 1st day. On the 5th day, serum creatinine levels decreased in both groups. The estimated GFRs were not significantly different between the two groups on the 1st day.

Safety results
Adverse reactions not mentioned.

Conclusion
The authors concluded that prophylactic theophylline, given early after birth, has beneficial effects on reducing kidney dysfunction in neonates with asphyxia. But that further studies are needed to confirm its usage in NICUs.

Assessor's comments:
Prophylactic theophylline is not standard treatment in neonates to prevent renal dysfunction and the results of this study not convincing

Mitra et al, 2005. (42)
Title: *Intravenous aminophylline for acute severe asthma in children over two years receiving inhaled bronchodilators*

Description
Cochrane review to determine whether addition of intravenous aminophylline produced a beneficial effect in children with acute severe asthma receiving oxygen, maximised inhaled bronchodilators and oral/intravenous glucocorticoids

Methods
Objective(s)
To determine if the addition of intravenous aminophylline produces a beneficial effect in children with acute severe asthma receiving conventional therapy.

Study design
Cochrane review.

Study population /Sample size

Seven trials met the inclusion criteria (380 participants).

Treatments
Intravenous aminophylline was given as an initial bolus, followed by a continuous infusion with serum levels checked to ensure “therapeutic levels” in all seven studies.

Outcomes/endpoints
Lung function, symptoms, medication use, length of hospital stay, PICU admission rates, adverse events and withdrawal.

Statistical Methods
Continuous data variables: Fixed Effect Weighted Mean Difference (WMD) for data measured on the same scale.
Data measured on different scales which could not be converted to a WMD, data were pooled using a Fixed Effect Standardised Mean Difference (SMD).
Dichotomous variables: pooled studies with a Fixed Effect Risk Ratio (RR). Risk difference and relative risk.

Results
Recruitment/ Number analysed
Seven trials, 380 participants.

Baseline data
The mean age of the children in all the studies but one was between 5 years and 9 years. In one studye the children were slightly older (mean age aminophylline group 11.5 years, placebo group 10.7 years)

Efficacy results
The addition of aminophylline to steroids and ß$_2$-agonist significantly improved FEV$_1$% predicted over placebo at 6-8 hours, 12-18 hours and 24 hours. Aminophylline led to a greater improvement in PEF % predicted over placebo at 12-18 hours. There was no significant difference in length of hospital stay, symptoms, frequency of nebulisations and mechanical ventilation rates.

Safety results
Treatment with aminophylline is associated with an increased risk of vomiting.

Conclusion
The review concluded that addition of intravenous aminophylline should be considered early in the treatment of children hospitalized with acute severe asthma with sub optimal response to the initial inhaled bronchodilator therapy. Although the improvement is sustained for 24 hours, there is no apparent reduction in length of hospital stay or number of inhaled beta2-agonists nebulisations.

Assessor’s comments:
In children with a severe asthma acute exacerbation, unresponsive to maximized bronchodilation, supplemental oxygen and systemic steroids, the addition of aminophylline/theophylline improves lung function.

Yung et al, 1998 (72)
Title: *Randomised controlled trial of aminophylline for severe acute asthma*

Description
Randomized controlled trial of theophylline as add-on to salbutamol in severe acute asthma in children.

Methods
Objective(s)
To determine whether children with severe acute asthma treated with large doses of inhaled salbutamol, inhaled ipratropium, and intravenous steroids are conferred any further benefits by the addition of aminophylline given intravenously.

Study design
Randomised, double blind, placebo controlled trial.

Study population /Sample size
163 children admitted to hospital with asthma who were unresponsive to nebulised salbutamol.

Treatments
Aminophylline infusions were given as a loading dose of 10 mg/kg infused over one hour, followed by a continuous infusion of 1.1 or 0.7 mg/kg/hour for subjects younger than 10 years and 10 years of age or older, respectively. Placebo infusions were given in the same fluid at the same volumes and rates.

Outcomes/endpoints
The first principal outcome measure was the length of stay in hospital. The second principal outcome measure was spirometry.

Statistical Methods
Treatment groups were compared by the unpaired Student's *t* test for normally distributed data and the Mann–Whitney U test for non-normally distributed data. Logarithmic transformations of skewed data were performed to make the data normally distributed where possible.

Results
Recruitment/ Number analysed
In total, 191 were eligible and 163 randomised. Intention to treat analysis.

Baseline data
Median age months 76.2 (theo)/ 74.2 (placebo). Sex 53/56 % males.

Efficacy results
No significant difference in length of stay. Aminophylline conferred clinically and statistically significant early benefits on airway function and oxygenation, sustained to 24 hours for oxygenation, but not for airway function, and reduced the risk of endotracheal intubation.

Safety results
The dose used in the study was associated with a significant risk of nausea and vomiting.

Conclusion

Assessor's comments:
The study is included in the Cochrane review mentioned above. Same conclusion: aminophylline have a place in therapy in the management of severe acute asthma in children unresponsive to initial treatment.

Roberts et al, 2003 (54)
Title: *Intravenous salbutamol bolus compared with an aminophylline infusion in children with severe asthma: a randomised controlled trial*

Description
A single bolus of salbutamol was compared with a continuous aminophylline infusion in children with severe asthma in a randomized double blind study.

Methods
Objective(s)
To compare the effectiveness of a short bolus of salbutamol with an aminophylline infusion in children and teenagers with severe asthma

Study design
Randomized double blind study

Study population /Sample size
Forty four subjects were enrolled, with 18 randomly allocated to receive salbutamol and 26 to receive aminophylline.

Treatments
Subjects were randomized to receive either a short intravenous bolus of salbutamol (15 µg/kg over 20 minutes) followed by a saline infusion or an aminophylline infusion (5 mg/kg over 20 minutes) followed by 0.9 mg/kg/h.

Outcomes/endpoints
Asthma severity score (ASS) at 2 hours, duration of oxygen therapy, length of hospital stay. Adverse events

Statistical Methods
Intention to treat. Wilcoxon rank sum test.

Results
Recruitment/ Number analysed
Sixty children were admitted with severe asthma during a cumulative recruitment period, Of these 44 were enrolled into the study (fig 1). Eighteen subjects (40.9%) were randomly allocated to treatment with a bolus of salbutamol and 26 (59.1%) to an aminophylline infusion.

Baseline data

Age (years) 3.85 (salbutamol) 4.12 (theophylline). Sex 66.7 % and 76.9 % males respectively.

Efficacy results
An intention to treat analysis showed that there was no statistically significant difference in the asthma severity score (ASS) at 2 hours between the two groups. There was a trend (p=0.07) towards a longer duration of oxygen therapy in the salbutamol group and a significantly (longer length of hospital stay in the salbutamol.

Safety results
There was no significant difference in adverse events between the two groups.

Conclusion
This study suggests that, in severe childhood asthma, there is no significant difference in the effectiveness of a bolus of salbutamol and an aminophylline infusion in the first two hours of treatment. Overall, the aminophylline infusion was superior as it significantly reduced the length of stay in hospital.

Assessor's comments:
Small study. Apparently *bolus* salbutamol equivalent in regard to efficacy to *infusion* of theophylline.

MAH 1 conclusion:
1. There is no identifiable pattern of treatment-emergent adverse events that would suggest any difference in the safety profile of theophylline in children from its known safety profile in adults.
2. The data presented show a positive benefit - risk balance of using theophylline based on the bodyweight dose recommendations in paediatric patients with respiratory disease.
   The lowest dose of theophylline prolonged release tablet produced by the MAH 1 is 200 mg which for a recommended maintenance dose of 9 mg/kg corresponds to an age of 7 years (approx 22 kg).

3. Discussion
MAH 1 has provided a wide range of published studies regarding the pharmacokinetics, efficacy and safety of theophylline in children. The study report from a single company sponsored Phase I clinical study did not contain additional information in relation to the use of theophylline in children.
The elimination of theophylline is markedly decreased in premature infants, due to an undeveloped CYP enzyme activity. Clearance is increased in later childhood to values above those observed in adult subjects. The rapid clearance in childhood decreases toward adult values in the late teens. Saliva samples instead of blood samples might be valuable.
A Cochrane review from 2005 concludes that children with a severe asthma acute exacerbation, unresponsive to maximized bronchodilation, supplemental oxygen and systemic steroids, the addition of theophylline improves lung function.

I. MAH 2 SANOFI-AVENTIS

I.1 Information on the pharmaceutical formulation used in the clinical study(ies)

The theophylline-containing medicinal product of the MAH 2, Solosin®, is marketed in three different pharmaceutical forms:

- prolonged-release tablets containing 270 mg and 135 mg theophylline, respectively
- oral drops / solution, containing 104 mg theophylline per ml solution [~ 24 drops]
- (concentrate for solution for infusion, containing 41.6 mg theophylline per ml solution

I.2 Non-clinical aspects

MAH 2 has not performed any non-clinical study on the toxicity of theophylline in juvenile animals or any further non-clinical trials specifically addressing its use in paediatrics.
No relevant published non-clinical trials addressing juvenile toxicity have been identified.

I.3 Clinical aspects

1. Introduction

Literature review

a. Pharmacokinetics – 7 studies
b. Controlled randomized studies – 12 studies
c. Meta-analyses - 1 study
d. Review article – 3 studies

Company sponsored clinical studies - none
MAH 2 has not performed any clinical study on theophylline in the paediatric population.

<u>Literature review</u>

1.a Pharmacokinetics

Aranda et al. 1976 (2)
Title: *Pharmacokinetic aspects of theophylline in premature newborns.*

Description
Pharmacokinetic study in premature infants

Methods
Objective(s)
To characterize the pharmacokinetics of theophylline in premature infants.

Study design
Pharmacokinetic study.

Study population /Sample size
Six premature infants treated with theophylline at day three and 15 days of age because of repeated episodes of apnoea and bradycardia.

Treatments
In five patients 3.2 – 4.0 mg/kg theophylline infusion in 20 minutes. In one patient 6.0 mg/kg divided in 3 doses.

Outcomes/endpoints
Capillary blood samples at times 0, 5, 15, 30 and 45 minutes, 1, 2, 4, 6 and 8 hours and then every 12 hours for three days. Pharmacokinetic parameters: clearance, half lives, volume of distribution, protein binding. Measures from whole blood, Vd and CL therefore expected to be slightly higher than the corresponding plasma values.

Statistical Methods
One-compartment model assumed. Ke and T½ computed from the slope. Vd = dose/C_0. Clearance = Ke * Vd.

Results
Recruitment/ Number analysed
Six premature infants.

Baseline data
Gestational age 25–32 weeks (mean 27.5 weeks). Birth weight 624–1200 g (mean 917 g).

Efficacy results
T½ varied from 14.4 – 57.7 hours. Vd 0.434 – 1.066 L/kg. CL 12.79 – 25.87 ml/kg/hour. At plasma concentration of theophylline of 17 mg/L 56.4 % was bound to adult plasma protein and 36.4 % bound to cord plasma protein.

Safety results
Loading dose: 5.5 mg/L, maintenance dose 1.1 mg/kg every eight hour would achieve and maintain blood concentration of 8mg/l (=plasma conc 10 mg/L).

Conclusion
Elimination of theophylline substantially slower in premature infants compared to older children and adults.
T½ nine times longer in premature than in children 1-4 years and CL seven times longer.

Assessor's comments:
The elimination of theophylline in premature infants is substantially slower than that seen in older persons.

Bellon et al. 1981 (5)
Title: *[Theophylline in childhood asthma. Pharmacokinetic and clinical study (author's transl)]*

Description
Paper in French. A pharmacokinetic study of both an intravenous and an oral dose of theophylline.

Methods
Objective(s)

To investigate the pharmacokinetics of theophylline in children.

Study design
Pharmacokinetic study

Study population /Sample size
Fourty children

Treatments
PK: An single intra-venous injection of an anhydrous theophylline. Dose = 4.24 ± 0.94 mg/ kg.
Absorption: 6 mg/kg theophylline syrup.
Long term treatment: 16 mg/kg.

Outcomes/endpoints
Pharmacokinetic parameters. Method not clear from the translated abstract.

Statistical Methods

Results
Recruitment/ Number analysed
Fourty children

Baseline data
Age 6 month -17 years. Ten girls and 30 boys.

Efficacy results
T 1/2 6.06 ± 2.53 hours; apparent Vd 0.585 ± 0.148 L/kg and CL 0.078 ± 0.35 L/kg/ hour. Absorption of the syrup was consistent, quick and complete.

Safety results
The correlation between the actual and calculated needs on the basis of theophylline clearance was poor.

Conclusion
The authors conclude that the correlation between the actual and calculated needs on the basis of theophylline clearance was poor and the proportion of patients with good clinical response to treatment was smaller than reported in the literature.

Assessor's comments:

Paper in French, only English summary. Pharmacokinetic parameters of theophylline estimated in children from 6 months to 17 years.

Brazier et al. 1980 (10)
Title: *Study of theophylline metabolism in premature human newborns using stable isotope labelling*

Description
To describe the identification of labeled caffeine and of its metabolites in the plasma and urine of two newborn preterm twins treated with labeled theophylline - as an indication of an alternative route of elimination in preterm neonates compared to adults.

Methods
Objective(s)
To study theophylline metabolism in premature newborns.

Study design
To identify labeled caffeine and its metabolites in the plasma and urine of preterm infants treated with labeled theophylline to study theophylline metabolism.

Study population /Sample size
Two twin premature human newborns with primitive apnea.

Treatments
A theophylline solution containing 46.5% labeled molecules and 53.5% unlabeled molecules was administered by nasogastric tube to two twin premature human newborns. Dose 3 mg/kg every 8 h, reduced to 2 mg/kg and increased again to 3 mg/kg.

Outcomes/endpoints
Blood was taken by heel prick 2 h after the theophylline administration on the morning of the lst, 2nd, 3rd, 4th, 5th, 7th, 8th, 9th, llth, 16th, 23rd and 26th days. Urine samples were collected for 24 h after administration on the same days.

Results
Recruitment/ Number analysed
Two twin premature human newborns

Baseline data
The birth weight and gestational age were respectively 1360g, 1380g and 32 weeks.

Efficacy results
Caffeine plasma levels showed the same variation as theophyllin. Labelled 1,7-DMX and 3,7-DMX were found in the urine of the infants, but 3-methylxanthine – a quantitatively important metabolite in adult urine was not detected in the urine of the infants.

Conclusion
The labeling of theophylline with stable isotopes has shown a new metabolic pathway for theophylline different from those observed in metabolism by adults. A part of the administered theophylline is methylated at the N-7 position to give caffeine.

Assessor's comments:
The study demonstrates that theophylline has a different metabolism in preterm infants compared to adults, which can explain the prolonged clearance and T½.

Ellis et al. 1976, (16)
Title: *Pharmacokinetics of theophylline in children with asthma.*

Description
Pharmacokinetic study in 30 children in the age of 6-17 years.

Methods
Objective(s)

To determine the total clearance and other pharmacokinetic characteristics of theophylline asthmatic children, with special emphasis on the assessment of the magnitude of inter-individual differences in the pharmacokinetic parameters.

Study design
Pharmacokinetic study. Intravenous injection of single dose in children with asthma and healthy adults for comparison.

Study population /Sample size
Thirteen inpatients and seventeen outpatients.

Treatments
A single dose of aminophylline (theophylline ethylenediamine), 4 mg/kg of body weight, was injected intravenously by infusion pump over three to five minutes.

Outcomes/endpoints
Blood samples were obtained before injection and 5, 15, 30, 60, 120, 240, 360, and 480 minutes after the end of the injection. Pharmocokinetic parameters: the distribution and elimination rate constants, the apparent volume of distribution, T½ and the total clearance.

Statistical Methods
The theophylline concentration data were fitted to a bi-exponential equation and the constants of this equation, obtained by nonlinear least-squares regression analysis, were used to determine the pharmacokinetic constants of a linear, two compartment open system.

Results
Recruitment/ Number analysed
Thirty asthmatic children,

Baseline data
Nineteen boys and eleven girls, ranging in age from 6.1 to 16.8 years (mean ± SD, 10.7 ± 2.6 years).

Efficacy results

TABLE I

SUMMARY OF PHARMACOKINETIC CONSTANTS FOR THEOPHYLLINE IN 30 CHILDREN

Constant	*Mean Value*	*SD*	*Range*
k_{12} (hr^{-1})	4.38	2.59	1.30 to 11.6
k_{21} (hr^{-1})	4.80	1.69	2.21 to 10.5
k_{el} (hr^{-1})	0.404	0.159	0.198 to 0.800
V_c (ml/kg)	225	66	110 to 361
V_{area} (ml/kg)	422	64	278 to 519
Biological half-life ($t_{1/2\beta}$) (hr)	3.69	1.13	1.42 to 7.85
Total clearance (ml/hr/kg)	87	35	30.6 to 221

TABLE II

SUMMARY OF PHARMACOKINETIC CONSTANTS FOR THEOPHYLLINE IN SIX ADULTS

Constant	*Mean Value*	*SD*	*Range*
k_{12} (hr^{-1})	4.66	2.99	1.25 to 8.63
k_{21} (hr^{-1})	4.68	2.10	1.65 to 7.32
k_{el} (hr^{-1})	0.259	0.092	0.158 to 0.434
V_c (ml/kg)	223	17	209 to 250
V_{area} (ml/kg)	448	86	342 to 589
Biological half-life ($t_{1/2\beta}$)	5.76	1.56	3.47 to 7.97
Total clearance (ml/hr/kg)	57	18	39.7 to 91.8

There was no statistically significant correlation between the value of the elimination rate constant and the age of the children and no statistically significant difference between the

boys and girls with respect to the apparent volume of distribution, biological half-life, and total clearance of theophylline.
The average value of the elimination rate constant in the children was significantly higher *(P* < .05 by Student's t-test) than in the adults and this is reflected by a shorter average biological half-life and higher average total clearance of theophylline in the children.

Safety results
There was considerable inter-individual variation in T½ and CL.

Conclusion
Theophylline is eliminated much more rapidly by children than by adults, on the average, and that (just as in adults) there are pronounced inter-individual differences in the total clearance of theophylline in children.

Assessor's comments:
Children eliminate theophylline more rapidly on the average than do adults and also show pronounced inter-individual differences in the elimination of the drug. Compared to adults, children (> 6 months) require relatively larger amounts of theophylline per day. Gender not significant factor regarding clearance.

Grygiel et al. 1980 (21)
Title: *Effect of age on patterns of theophylline metabolism.*

Description
Study of pattern of excression of theophylline in premature neonates, children and adults.

Methods
Objective(s)
To study the pattern of excretion of urinary theophylline and theophylline metabolites in premature neonates, children and adults.

Study design
Pharmacokinetic study of the elimination of theophylline.

Study population /Sample size
Six premature neonates treated for neonatal apnea, 16 children treated for acute asthma and 14 adults treated for acute exacerbation of obstructive airways disease. Non-smoking for 2 years.

Treatments
Standard dose of theophylline i.v. 10mg/kg/day

Outcomes/endpoints
Urine collected over a dosing interval on a single occasion from adults and children and weekly from neonates. Trough blood sample at the end of each urine period.
Trough plasma theophylline concentrations corrected for weight and dosages (Cp), urinary theophylline and theophylline metabolites (IMU, 3MX, 1MX, DMU and caffeine).

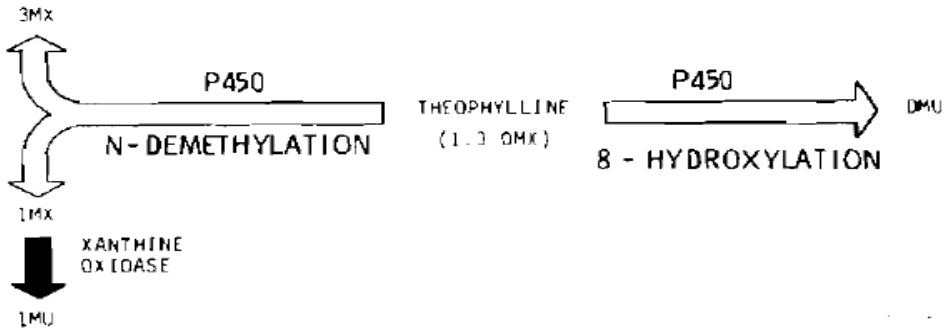
Statistical Methods
Difference between groups assessed by unpaired Student's t test, associations analyzed by least-squares linear regression.

Results
Recruitment/ Number analysed
Six premature neonates, 16 children, 14 adults. Unclear recruitment procedure.

Baseline data
Neonates (3 M, 3 F), gestational age 28 – 32 weeks, birth weight 0,8 – 1,62 kg. Children (12 male, 4 female) age 2-12 years. Adults (9 male, 5 female) 20-65 years.

Efficacy results
When adjusted to a standard dose of 10 mg/kg/ day, there were significant differences in corrected plasma levels of theophylline between the groups (children < adults < premature neonates).
In the premature 98 % of the total theophylline was excreted unchanged and 2 % as caffeine. IMU, 3MX, 1MX, DMU was not detected.
In the children and the adults there was a positive correlation between urinary excretion of IMU and 3MX, but both 3MX and IMU correlated negatively with DMU.

Conclusion
The positive correlation between 1MU and 3MX and the negative correlation between 3MX, IMU and DMU suggest that there are two different metabolic pathways (N-demethylation and 8-hydroxylation) carried out by different forms of cytochrome P-450 enzymes.



Assessor's comments:
The metabolism of theophylline involves two different pathways, probably two different CYP enzymes, both are enhanced in children, but absent in premature neonates, at least up to 40 weeks of gestation.

Kelly et al. 1980 (33)
Title: ***Efficacy of a 12-hour sustained-release preparation in maintaining therapeutic serum theophylline levels in asthmatic children***

Description
Study in 20 children with asthma to test if a sustained-release theophylline formulation Could maintain theophylline levels within the therapeutic interval (10 – 20 ug/ml).

Methods
Objective(s)

To determine whether a new sustained-release theophylline preparation TheoDur could maintain therapeutic serum theophylline levels in asthmatic children on a 12-hour dosage regimen.

Study design
Ability of sustained release formulation to maintain therapeutic serum levels.

Study population /Sample size
Twenty asthmatic children, who required continuous theophylline for control of their asthma.

Treatments
Sustained release tablets of 100mg, 200mg and 300mg tablets required to achieve a therapeutic level (a six hour post dose level between 10 and 20 µg/ml)

Outcomes/endpoints
Serum theophylline concentrations. Blood samples were drawn immediately prior to a dose, then every three hours for 24 hours (two dosing intervals).

Statistical Methods

Results
Recruitment/ Number analysed
All 20 patients were referrals to the University of New Mexico Pediatric Pulmonary Center.

Baseline data
Age 6 – 18 years, mean 11,4 years. Twelve boys and eight girls.

Efficacy results
The patients required a mean ± SEM dosage of 10.0 ± 0.54 mg/kg/dose to achieve therapeutic serum theophylline levels. Patients in the six- to nine-years age group required a mean dosage of 10.3 ± 0.87 mg/kg/dose, while patients ten to 18 years of age required a mean dosage of 9.7 ± 0.72 mg/kg/dose. This dosage resulted in a mean six-hour postdose serum theophylline level of 15.65 ± 0.72 ug/ml.
The mean ± SEM difference between maximum and minimum serum theophylline levels for the group was 4.5 ± 0.3 ug/ml.

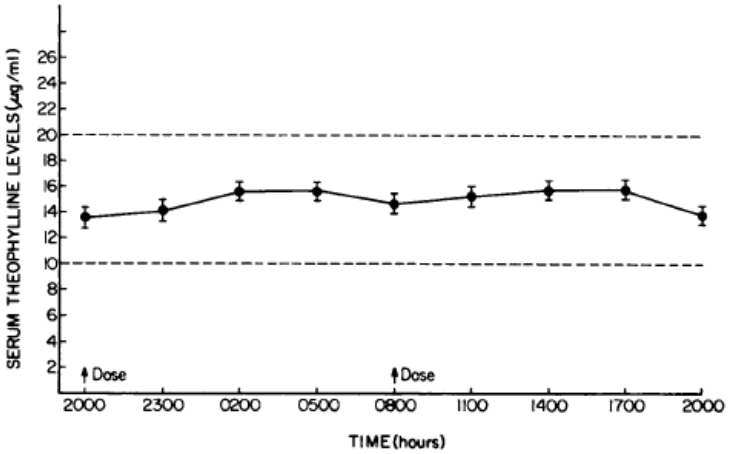


Figure. Mean ± SEM 24-hour serum theophylline levels for 20 asthmatic children on a mean TheoDur dosage of 10.0 ± 0.54 mg/kg/dose every 12 hours.

Conclusion
The sustaine-release theophyllin preparation can maintain therapeutic serum theophylline levels with minimal fluctuations in asthmatic children on a 12-hour dosing schedule. Less frequent dosing could increase patient compliance.

Assessor's comments:
Sustained release preparation with twice a day dosing maintained serum theophylline levels within therapeutic interval.

Sarrazin et al. 1980 (56)
Title: *Dose-dependent kinetics for theophylline: observations among ambulatory asthmatic children*

Description
Retrospective study with review of the charts of asthmatic children to examine the change in serum theophylline concentration with change in dosage.

Methods
Objective(s)
To examine the relationship between serum concentration and daily dosage of theophylline to assess the clinical impact of dose-dependent kinetics.

Study design
Population pharmacokinetic study. Retrospective study.

Study population /Sample size
Children with chronic asthma in continuously treatment with theophylline. Initially review of 200 charts to identify patients with >1 serum theophylline measurement with different dosage. Retrospective review of 500 charts revealed revealed 26 patients with at least three steady state serum theophylline concentrations at three different doses.

Treatments
A completely bioavailable slow-release formulation of theophylline.

Outcomes/endpoints
Theophyline serum concentrations at steady state with different theophylline doses.

Statistical Methods

Results
Recruitment/ Number analysed
Twenty-six patients out of 500 with > 2 serum theophylline concentration measurements with different theophylline dosing.

Baseline data
Not reported.

Efficacy results
Twenty-one of the 26 patients had disproportional relationship between theophylline dose and serum concentration, indicating non-linear elimination. Thirty patients (15 %) of the

initial 200 charts had changes in serum concentration that were 50 % or greater than the change i dose (non-linearity).

Safety results
Non-linear dose dependent kinetics for at least 15 % in the study population.

Conclusion
Clinically important dose-dependent kinetics for theophylline occurs in at least 15 % of children.

Assessor's comments:
Dose dependent kinetics may have clinical importance in some children. This emphasizes that theophylline should be dosed according to serum concentrations.

a. Controlled randomized studies

Rachelefsky et al. 1980 (51)
Title: ***Metaproterenol and theophylline in asthmatic children.***

Description
Clinical study of the efficacy and safety of theophylline and a beta 2 selective agonist (metaproterenol) in asthmatic children..

Methods
Objective(s)
To compare the efficacy and safety of theophylline and metaproterenol in the daily management of the asthmatic child and to determine if metaproterenol alone could be considered a primary drug of choice.

Study design
Randomized, double-blind, crossover study

Study population /Sample size
Twenty children with a diagnosis of bronchial asthma requiring daily medication.

Treatments
Four weeks treatment with theophyllin + placebo or metaproterenol + placebo. Theophylline sustained-release tablets every eight hours to maintain a theophylline level between 10-20 ug/ml (four hours post-drug administration). The 24-hour dose of theophylline required ranged from 12 to 30 mg/kg with a mean of 18.3 (± 5. 7 S.D.). Metaproterenol dose (tablet formulation 10 mg per dose for those under 60 pounds and 20 mg per dose for those over 60 pounds) administered three times a day.

Outcomes/endpoints
Daily dairy card (wheeze,cough, chest tights, shortness of breath, attacks), FEV1 and FEF, peak flow.

Statistical Methods
The effectiveness of the two drugs was compared testing the median differences with the Wilcoxon signed rank test. Time trends within the four-week periods were examined by

plotting weekly values. Statistical tests were done by applying the Wilcoxon signed rank test to differences between weeks 1 and 4.

Results
Recruitment/ Number analysed
Twenty subjects

Baseline data
Twelve males and eight females. Age range 7-15 years (mean 10.7 years ± 2.7 S.D.). Mean duration of asthma was 8.6 years (± 3.4 S.D.) range 2-14 years.

Efficacy results
THEO to be statistically superior, but not necessarily clinically superior when evaluating day and night-time cough, number of daytime attacks, extra doses of medication and morning, midday and bedtime peak expiratory flow rate (PEFR).

Safety results
Side effects more common with theophylline.

Conclusion
The authors conclude that metaproterenol may be an alternative to theophylline in the management of chronic asthmatic children.

Assessor's comments:
A beta 2 selective agonist is an adequate alternative to theophylline in the treatment of asthmatic children requiring daily bronchodilators as it has less side effects and the efficacy is equivalent.

Meltzer et al. 1992 (41)
Title: *Long-term comparison of three combinations of albuterol, theophylline, and beclomethasone in children with chronic asthma*

Description
Company sponsored (Glaxo) 12-week study of different therapeutic regimens in children with chronic, moderately severe asthma.

Methods
Objective(s)
To compare three different combinations of inhaled beta-agonist, oral theophylline and inhaled glucocorticosteroids during a 3-month period in children with chronic asthma.

Study design
Multicenter doubleblind, randomized, parallel group study.

Study population /Sample size
In total, 111 children with chronic asthma.

Treatments
Three combination regimens:
1) Inhaled albuterol 180 µg q.i.d.and oral theophylline b.i.d.
2) Inhaled albuterol, inhaled beclomethason 84 µg q.i.d.

3) Inhaled albuterol, inhaled beclomethason, oral theophylline
Theophylline dose adjusted until serum level of 8-18 ug/ml. Baseline visit when theophylline level was in the therapeutic range.

Outcomes/endpoints
Symtpom scores, daytime activity, quality of sleep, peak flow, concomitant medication and adverse effects.

Statistical Methods
The van Elteren method, Cochrane-Mantel-Haenszels,Chi-square and Fishers exact test.

Results
Recruitment/ Number analysed
Of the 111 patients enrolled 88 completed the 12 weeks of therapy. Significantly more patients in the albuterol/theophylline stopped because of exacerbations of asthma.

Baseline data
Age 6 – 16 years mean 10 years. 31% females.

Efficacy results
Improvement in all three treatment groups. Significantly greater improvement in all symptoms and less use of concomitant medication in both groups receiving beclomethasone.

Safety results
No difference in the incidence of adverse events.

Conclusion
The study support the view that optimal pharmacotherapy for children with chronic asthma should include topical anti-inflammatory agents, such as inhaled corticosteroids.

Assessor's comments:
Theophylline is inferior to corticosteroids in children with asthma.

Bien et al. 1992 (7)
Title: ***Intravenous theophylline in pediatric status asthmaticus. A prospective, randomized, double-blind, placebo-controlled trial***

Description
Placebo controlled study to test the hypothesis: Intravenous theophylline does not provide a clinically significant benefit when added to inhaled albuterol and intravenous methylprednisolone in the treatment of pediatric status asthmaticus.

Methods
Objective(s)
To determine whether intravenous theophylline, added to inhaled albuterol and intravenous methylprednisolone, provides a clinically significant benefit in the treatment of pediatric status asthmaticus.

Study design
Prospective, randomized in blocks of 20, placebo-controlled, double-blind study.

Study population /Sample size
Children of 2-10 years of age, diagnosed with asthma and with asthmatic exacerbation requiring admission to the hospital.
Fourty-four patients were enrolled and 39 were available for data analysis. The authors note that 220 patients would have to be included in order to detect a statistically, but not clinically significant difference of 1 in pulmonary index (PI). The latter would require 50,000 participants.

Treatments
Continuous i.v. infusion of theophylline or placebo. 1.6mg/ml; i.v. Methyl-prednisolone 2mg/kg push at enrollment, and 1 mg/kg every 6 hours thereafter; aerosolized salbutamol as needed (2.5 mg/2.5 ml).
The study period consisted of the first 24 hours of hospitalization.

Outcomes/endpoints
Pulmonary Index (PI) (respiratory rate, wheezing, inspiratory/expiratory ratio, accessory muscle use), oxygen saturation, peak flow, theophylline levels.
Patients were evaluated every 7-9 hours.

Statistical Methods
Demographic data were analyzed with chi-square and Student's t-test. PI and aerosol data were treated as continuous variables and analyzed using nested analysis of variance.

Results
Recruitment/ Number analysed
Twenty in placebo group and nineteen in the theophylline group.

Baseline data
Age: 49 months in the placebo group and 69 months in the theophylline group.
PI 6.5 – 7,

Efficacy results
The improvement of PI scores over time did not differ between groups.

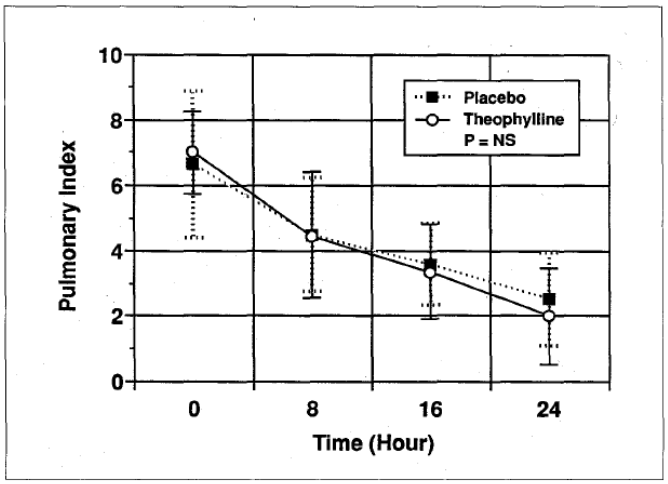


Figure 2. Pulmonary index over time. Measure of clinical asthma score, or pulmonary index, in theophylline and placebo groups at each evaluation point. There was no significant difference between the two groups.

Safety results
Theophylline group patients experienced more nausea, emesis and complaints of insomnia.

Conclusion
The authors conclude that there is no benefit in adding theophylline to treatment with methylprednisolone and albuterol for pediatric status asthmaticus. Furthermore, there are significantly more adverse effects associated with the use of theophylline.

Assessor's comments:
Theophylline does not provide a clinical benefit when added to treatment with methylprednisolone and beta-agonist in status asthmaticus.

Zimmermann et al. 1992 (74)
Title: *Randomized Cross-Over Trial Salbutamol Controlled Release (SCR) vs. Theophylline Retard (THR) in Children with Asthma.*

Description
Short English summary of study of randomized cross-over trial in Swiss journal.

Methods
Objective(s)
To compare the efficacy of salbutamol controlled release vs. theophylline retard in children with asthma.

Study design
Randomized cross-over trial. Blinding not mentioned.

Study population /Sample size
Sixty-six patients, 60 % with a mixed form of asthma (?)

Treatments
Controlled release salbutamol or theophylline retard. Doses not mentioned.

Outcomes/endpoints
Improvement/no change/worse. FEV1.

Statistical Methods
Unclear

Results
Recruitment/ Number analysed
Siwty-six patients, 7 dropped out early, 3 due to side effects.

Baseline data
Eleven female and 55 males. Age 8 ±2 years

Efficacy results
Improved: 23 salbutamol / 12 THEO
No change: 22 salbutamol / 28 THEO

Worse: 11 salbutamol / 15 THEO

Safety results

Conclusion
The authors state that since treatment with salbutamol needs no drug-monitoring and the clinical judgement showed some superiority for salbutamol, this should be regarded as an advantageous alternative to theophylline.

Assessor's comments:
Sparse information, but salbumatol probably superior to theophylline in children with asthma due to a wider therapeutic index.

Carter et al. 1993 (12)
Title: *Theophylline in acute asthma.*

Description
Clinical study in children with severe acute asthma to investigate the role of theophylline in addition to treatment with inhaled beta-agonist and intravenous methylprednisolone.

Methods
Objective(s)
To determine whether intravenously administered theophyllline, when added to frequently nebulized albuterol and intravenously administered methylprednisolone, benefits children hospitalized with severe asthma.

Study design
Prospective, randomized, placebo-controlled, parallel-group, double-blind study.

Study population /Sample size
Children 5 to 18 years of age with severe asthma admitted to treatment at a tertiary-care teaching hospital.

Treatments
All patients received 2.5 to 5.0 mg of nebulized albuferol every 20 minutes to every 6 hours, intravenously administered methylprednisolone (1 mg/kg every 6 hours), and either intravenously administered theophylline (as aminophyiline) or placebo for 36 hours. Serum theophyiline concentrations were maintained between 10 and 20 ug/ml.

Outcomes/endpoints
FEV1 and clinical scores (respiratory rate, wheezing, inspiratory/expiratory ratio, and accessory muscle use). The total number of nebulizations, total albuterol dosage, adverse effects, and duration of hospital stay.

Statistical Methods
Fishers exact tst, Wilcoxon rank sum test. Differences in FEVI between the two groups at each time point were analyzed by repeated measures analysis of variance.

Results
Recruitment/ Number analysed
Twenty-five patients enrolled, 21 completed the study, nine placebo and 12 theophylline.

Baseline data
Theophylline(12 ptt) : age 12 years ±4, 8 male
Placebo (9 ptt): age 11 ±4, 6 male

Efficacy results
There were no significant differences between the groups in FEVI or clinical score at any of the measured time points. There were no significant differences in rate of improvement in FEVI, total number of nebulizations, total albuterol dosage, or duration of hospital stay.

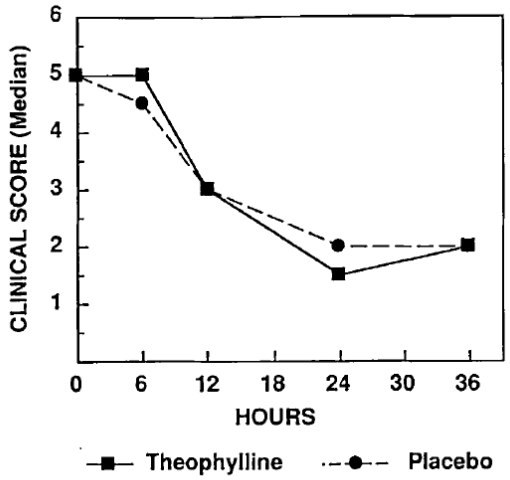


Fig. 3. Median clinical score at each measured time point for patients receiving theophylline (■) or placebo (●). There were no significant differences in median clinical scores between the groups at any of the time points (Wilcoxon rank sum test). The clinical score was determined by separately grading respiratory rate, inspiratory/expiratory ratio, wheezing, and chest retractions on a scale of 0 to 3 and then summing the individual grades to give the final score (0 to 12, with 0 indicating no symptoms and 12 indicating greatest severity).

Safety results
Adverse effects were mild and infrequent and did not differ significantly between the two groups.

Conclusion
Theophylline, at therapeutic concentrations, did not additionally benefit children hospitalized with severe asthma who were being treated frequently with nebulized albuterol and with methylpredniso!one intravenously.

Assessor's comments:
The risks associated with the improper use of theophylline are so substantial that it would be prudent not to subject all children hospitalized with asthma to this drug. However, theophylline may have a role in the treatment of those children who are not responding adequately to nebulized albuterol and corticosteroids.

DiGiulio et al. 1993 (14)
Title: ***Hospital treatment of asthma: lack of benefit from theophylline given in addition to nebulized albuterol and intravenously administered corticosteroid.***

Description

Clinical study in children with mild to moderate acute asthma to investigate the role of theophylline in addition to treatment with inhaled beta-agonist and intravenous methylprednisolone.

Methods

Objective(s)

To determine the efficacy of theophylline when given in addition to nebulized albuterol and intravenously administered corticosterold to children hospitalized with mild to moderate asthma.

Study design

Randomized, prospective, placebo-controlled, double-blind trial.

Study population /Sample size

Twenty-nine patients with asthma between the ages of 2 and 16 years completed the study. Hospitalized with non-life-threatening acute asthma.

Treatments

All patients received intravenously administered methylprednisolone and nebulized albuterol. The treatment group received theophylline 4,8 mg/kg and the placebo group dextrose in water. When intravenously administered medications were discontinued, therapy continued with oral administration of theophylline (or placebo) and of prednisone.

Outcomes/endpoints

The primary outcome variable was the number of hospital hours elapsed until an asthma score of ~2 was achieved. Clinical scores (respiratory rate, wheezing, inspiratory/expiratory ratio, and accessory muscle use). The patients could not cooperate to an acceptable peak flow test.

Statistical Methods

Group means were compared with the unpaired Student t test. Chi-square analysis was used to compare differences in nominal variables. Linear regression was used to compare the rate of symptom improvement with time. The two-sample median test was used to compare median values.

Results

Recruitment/ Number analysed

Thirty-four were enrolled and 29 completed the study.

Baseline data

There were no differences between the theophylline and placebo groups with respect to the patients' age (mean6.9 ±4.0 vs 7.4 ±3.6) or gender (69% vs 69% male). Most (86%) subjects were black,

Efficacy results

Time required to reach study discharge criteria and the rate of improvement of the clinical asthma score were not significantly different between the theophylline and placebo groups. The number of albuterol aerosol treatments required was not significantly different between groups.

Safety results

The adverse effects experienced were not significantly different between groups

Conclusion
When the combination of systemically administered corticosteroid and inhaled albuterol is used in the treatment of children hospitalized with mild to moderate asthma, addition of theophylline may not be justified.

Assessor's comments:

One of several small studies that does not find an advantage of adding theophylline to an inhaled beta-adrenergic agonist and corticosteroid for the treatment of children with mild to moderate acute asthma.

Needleman et al. 1995 (46)
Title: *Theophylline does not shorten hospital stay for children admitted for asthma.*

Description
Clinical study in children with acute exacerbation of asthma to investigate the role of theophylline in addition to treatment with inhaled beta-agonist and intravenous methylprednisolone.

Methods
Objective(s)
To determine if the use of intravenous theophylline, in the form of aminophylline, when added to systemic corticosteroids and aerosolized beta2-agonists, enhances the improvement of children with acute asthma exacerbations.

Study design
A double-blind, placebo-controlled, randomized, clinical trial.

Study population /Sample size
Forty-two children, aged 2 to 18 years, admitted to the hospital for acute exacerbations of asthma.

Treatments
Intravenous theophylline to maintain a serum level greater than 55 umol/L or a placebo infusion. All patients received methylprednisolone and nebulized albuterol.

Outcomes/endpoints
Major outcome measures were length of stay and the clinical score. Attempts were made to gather spirometri data and pulse oximetry as well.

Statistical Methods
Statistical significance was assessed by the use of a two-sided t-test.

Results
Recruitment/ Number analysed
Forty-five patients were enrolled in the study, and 42 (including 20 controls) completed it.

Baseline data

Efficacy results

Both groups in our study stayed in the hospital the same amount of time, and their clinical scores improved at the same rate.

Safety results
Theophylline's narrow therapeutic range mandates close monitoring and may have adverse effects.

Conclusion
These data suggest that the addition of theophylline to albuterol and corticosteroids does not enhance improvement of children admitted to the hospital with asthma.

Assessor's comments:
One of several small studies that does not find an advantage of adding theophylline to an inhaled beta-adrenergic agonist and corticosteroid for the treatment of children with mild to moderate acute asthma.
Or as the Dr Catherine D DeAngelis states in Editor's note: "In short, theophylline adds nothing but time, cost, and aggravation to the child, who's already in distress. Primum non nocere. Yes, siree!"

Yung et al. 1998 (72)
Title: *Randomised controlled trial of aminophylline for severe acute asthma.*

Study also submitted by MAH 1.

Assessor's comments:
Conclusion: aminophylline have a place in therapy in the management of severe acute asthma in children unresponsive to initial treatment.

Ream et al. 2001 (53)
Title: *Efficacy of IV theophylline in children with severe status asthmaticus.*

Description
Clinical study to examine if theophylline adds benefit to the treatment of children with severe status asthmaticus.

Methods
Objective(s)
To determine whether adding IV theophylline to an aggressive regimen of inhaled and IV b-agonists, inhaled ipratropium, and IV methylprednisolone would enhance the recovery of children with severe status asthmaticus admitted to the pediatric ICU (PICU).

Study design
A prospective, randomized, controlled trial

Study population /Sample size
Fourty-seven admissions (43 children) with severe status asthmaticus admitted to the pediatric ICU (PICU) of an urban, university-affiliated, tertiary-care children's hospital.

Treatments
All subjects initially received continuous albuterol nebulizations; intermittent, inhaled

ipratropium; and IV methylprednisolone. The theophylline group was also administered infusions of IV theophylline to achieve serum concentrations of 12 to 17 mg/L.

Outcomes/endpoints
Changes clinical asthma score (CAS), including oxygenation, inspiratory breath sounds, accessory muscles, expiratory wheezing, cerebral function. Time to reach a CAS of ≤ 3. A secondary measure was the time required to meet predetermined criteria for discharge from the PICU

Statistical Methods
Independent t-test, Fisher's exact tests, chi square and Kaplan Meier analysis.

Results
Recruitment/ Number analysed
Out of 4,520 patients admitted to the PICU in the 5-year study period, 320 had status asthmaticus, hereof 45 children (49 admissions) in severe status asthmaticus eligible for the study. Two were withdrawn. For unknown reasons the authors exclude patients receiving mechanical ventilation.

Baseline data
Age: thirteen months to 17 years. The patient characteristics are tabulated in regard to admissions, not patients. The patient admitted three times are therefore also counted three times.

Efficacy results
Among the 41 subjects (admissions?) who were not receiving mechanical ventilation, those receiving theophylline achieved a CAS of <3 sooner than control subjects (18.662.7 h vs 31.164.5 h; p<0.05). Theophylline had no effect on the length of PICU stay or the total incidence of side effects.

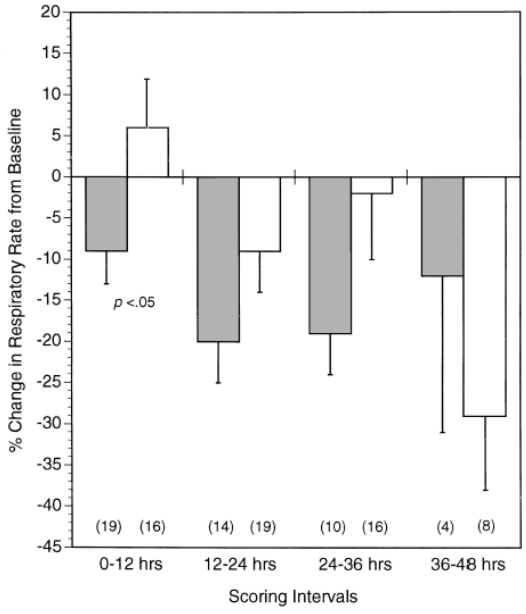


FIGURE 2. Bar graph comparing the effect of theophylline infusion on the percentage reduction in baseline respiratory rate. Data have been pooled in 12-h intervals over the first 48 h of PICU admission. Stippled bars represent the treatment group, and open bars represent control subjects. The number of observations in each group is indicated in parenthesis underneath each bar. Error bars represent 1 SEM.

Safety results

Subjects receiving theophylline had more emesis ($p<0.05$), and control patients had more tremor ($p<0.05$).

Conclusion
The authors conclude that theophylline safely hastened the recovery of children in severe status asthmaticus who were also receiving albuterol, ipratropium, and methylprednisolone and argue that the role of theophylline in the management of asthmatic children in impending respiratory failure should be reexamined.

Assessor's comments:
Overall, the author's conclusion cannot be supported. The study is unblinded. The only significant result is in a selected group of patients (or admissions) not receiving mechanical ventilation.
If theophylline has a role in the treatment of children unresponsive to basic treatment is unclear

Suessmuth et al. 2003 (61)
Title: *Low-dose theophylline in childhood asthma: a placebo-controlled, double-blind study*

Description
Theophylline in moderate childhood asthma.

Methods
Objective(s)
To study the clinical and immunomodulatory effect of theophylline in children with moderate, persistent asthma on regular inhaled corticosteroids (ICS).

Study design
Placebo-controlled, double-blind study. After a 6-week run-in period, patients received either theophylline or placebo for 12 weeks.

Study population /Sample size
Thirty-six patients with moderate, persistent asthma on regular ICS

Treatments
Theophylline 10 mg/kg bodyweight or placebo. In the treatment group, mean serum theophylline
was 7.1 mg/l.

Outcomes/endpoints
Diary cards, lung function, peripheral blood lymphocyte subpopulations and serum eosinophil cationic protein (sECP) were assessed

Statistical Methods
Differences within patients groups between study visits were analyzed using Student's paired t-tests. Differences between groups were analyzed using unpaired t-tests.

Results
Recruitment/ Number analysed

Thirty-six patients were recruited, three withdrew consent. Results are from the intention-to-treat group.

Baseline data
Mean age 12.5 SD 2.4 years. 29 male, 7 female.

Efficacy results
There was no change in symptoms or use of rescue medication. Mean (SD) peak expiratory flow (PEF) increased from 86% (24) to 95% (18) predicted. sECP decreased from 43.2 ug/l (32.5) to 26.5 ug/l (16.9) (p = 0.02). Lymphocyte subpopulations did not change.

Safety results
One of the patients in the theophylline group reported nausea and vomiting as a reason for withdrawal. There were no other reported adverse effects.

Conclusion
The study failed to show a beneficial clinical or an immunomodulatory effect of theophylline when used in low doses. These results do not support a more important role of theophylline in the long-term treatment of moderate childhood asthma.

Assessor's comments:

Theophylline level below therapeutic interval (10-20 mg/L) and probably problems with treatment compliance. Nevertheless, no significant clinical or anti- inflammatory effect observed in adding theophylline to low- to moderate dose ICS in moderate childhood asthma.

Wheeler et al. 2005 (70)
Title: *Theophylline versus terbutaline in treating critically ill children with status asthmaticus: a prospective, randomized, controlled trial.*

Description
Add-on of theophylline, terbutaline or both in critically ill children with status asthmaticus.

Methods
Objective(s)
To compare the efficacy of theophylline, terbutaline, or theophylline combined with terbutaline treatment in critically ill children with status asthmaticus who are already receiving continuous nebulized albuterol and intravenous corticosteroids.

Study design
Randomized, prospective, controlled, double-blind trial.

Study population /Sample size
Forty critically ill children between the ages of three and 15 years admitted to a paediatric intensive care unit of a tertiary-care children's medical center with impending respiratory failure secondary to status asthmaticus.

Treatments

All patients received intravenous methylprednisolone and continuous nebulized albuterol. The three study groups received theophylline plus placebo (group 1), terbutaline plus placebo (group 2), or theophylline and terbutaline together (group 3).

Outcomes/endpoints
Change in clinical asthma score over time, length of pediatric intensive care unit stay, and incidence of adverse events.

Statistical Methods
The differences in mean clinical asthma score (CAS) among the three groups at each time point were analyzed by repeated measures ANOVA.

Results
Recruitment/ Number analysed
Of the initially 336 patients only 40 children with severe status asthmaticus, representing 40 separate admissions to the PICU, qualified and were enrolled in the study. Reason for exclusion: #168 admission during the night, #80 CAS<7, #30 exclusion criteria, #19 lack of parent consent.

Baseline data

	Group 1	group 2	Group 3
Age, months	108±13	113±16	117±13
Male gender (%)	9 (70)	11 (70)	7 (60)
CAS	8.8±1.0	8.3±1.3	8.7±1.1

Efficacy results
There were no differences in clinical asthma score over time, length of pediatric intensive care unit stay, or incidence of adverse events between the three groups, with the exception of a higher incidence of nausea in children in group 3.

Safety results
The incidence of adverse events was similar between the groups.

Conclusion
The authors conclude that theophylline, when added to continuous nebulized albuterol therapy and intravenous corticosteroids, is as effective as terbutaline in treating critically ill children with status asthmaticus. The addition of theophylline to baseline therapy is more cost-effective when compared with terbutaline alone or terbutaline and theophylline together. The authors suggest that theophylline should be considered for use early in the management of critically ill asthmatic children.

Assessor's comments:
The study is not placebo-controlled. Only 10 % of eligible patients ended up enrolled in study. Terbutaline not superior to theophylline as add-on in critically ill children with status asthmaticus.

Radwan et al. 2010 (52)
Title: ***Effect of different monotherapies on serum nitric oxide and pulmonary functions in children with mild persistent asthma.***

Description

Small open study of controller mediciation, including theophylline for mild, persistent asthma.

Methods

Objective(s)

To evaluate monotherapy with either inhaled steroids, oral leukotriene receptor antagonist or theophylline in Egyptian children with mild persistent asthma by determining their clinical, laboratory and spirometric responses to treatment.

Study design

Open, randomized parallel group study.

Study population /Sample size

Thirty-nine children diagnosed as having mild persistent asthma and were attending the Allergy Clinic of Children's Hospital, Cairo University for routine visits.

Treatments

Group 1: oral leukotriene receptor antagonist (montelukast), Group 2: inhaled corticosteroid (fluticasone propionate), group 3: sustained-release (SR) theophylline, and group 4: no treatment. Theophylline levels not reported.

Outcomes/endpoints

Pulmonary function testing was performed at the start of therapy and 8 weeks later using spirometry. Eosinophil count and serum nitric oxide were estimated in the blood.

Statistical Methods

One-way analysis of variance (AN OVA) was performed to test the equality of the means of different treatments. Tukey's method was used to compare all pair wise differences between level means. The relationship between studied parameters was assessed using Pearson's linear correlation coefficient (r).

Results

Recruitment/ Number analysed

Thirty-nine asthmatic children

Baseline data

Twenty females and 19 males between the ages of eight and 13 years.

Efficacy results

Significant improvement in FEV1% in groups 1 (montelukast) and 3 (theophylline), Otherwise significant improvement in outcomes in group 1 (montelukast) and 2 (inhaled corticosteroid).

Safety results

Not reported.

Conclusion

The authors state that inhaled corticosteroid seems to yield the best response, but further larger studies are needed to validate the findings. The authors argue that mild persistent asthma in children should be treated with a controller medication, and that theophylline may be a good cost-benefit alternative for low socioeconomic groups of patients

Assessor's comments:
Small, open study. Theophylline may be a good cost-benefit alternative in countries of low socioeconomic income , but this raise safety issues in terms of need for individual dosing based on serum measurements.

b. Meta-analyses

Goodman et al. 1996 (20)
Title: *Theophylline in acute childhood asthma: a meta-analysis of its efficacy.*

Description
Meta-analysis of six randomized controlled trials to establish the efficacy of theophylline acute childhood asthma.

Methods
Objective(s)
to review systematically the published randomized clinical trials of theophylline efficacy in the context of standard therapy in children hospitalized with acute asthma.

Study design
MEDLINE search with the following search language: (aminophylline (mh) *or* theophylline (mh)) and (asthma (mh) or bronchial spasm (mh)) *and* not foreign (la).

Study population /Sample size
Six published trial of altogether 164 subjects from 1.5 to 18 years.

Treatments
Randomly allocation to treatment or comparison groups with double blinding. Patients in the treatment groups received either an intravenous (IV) theophylline or aminophylline bolus followed by continuous infusion. In five studies the control groups received IV saline or dextrose solution and in one study they received IV albuterol. All patients received IV corticosteroids with a methylprednisolone dose-equivalence ranging from 2.2 to 8.3 mgkg in the first 24 hours. In five of the six studies, serum theophylline levels were monitored.

Outcomes/endpoints
The *effect difference* (the difference between the mean or median value for the theophylline and the control groups) and the *percent effect difference* (the percent difference between the mean or median value for the theophylline and the control groups).

Statistical Methods
An effect was assigned a positive value if the theophylline group benefited. Effect size was calculated as a measure of the difference between the groups standardized by the variance. Test for homogeneity.

Results
Recruitment/ Number analysed
Six published trial of altogether 164 subjects.

Baseline data
1.5 to 18 years

Efficacy results
Pulmonary function parameters [forced expired volume in 1 second (FEV,), forced expired flow (FEF)] appeared better at 24 hours in the theophylline group, but the results did not reach statistical significance (mean effect difference,+3.9% predicted values; pooled effect size, +1.6 SDS; ***P*** = 0.25).

Safety results
Greater number of albuterol treatments required and the longer hospital stays in the theophylline group suggest disadvantageous effect.

Conclusion
The authors conclude that the data do not indicate a significant beneficial effect of theophylline in children hospitalized with acute asthma. There is evidence for weak detrimental effects. Theophylline efficacy in intensive care unit settings remains unstudied

Assessor's comments:
Theophylline did not have an additive effect to corticosteroids, and is not indicated as add-on in children hospitalized with acute asthma, unless unresponsive to standard therapy.

c. Reviews

Self et al. 2002 (58)
Title: *Reassessment of theophylline use for severe asthma exacerbation: is it justified in critically ill hospitalized patients?*

Description
Review of randomized clinical trials in hospitalized patients – not only children - with asthma exacerbation where theophylline is added to standard therapy.

Methods
Objective(s)
To review double-blind, randomized, placebo-controlled trials examining the efficacy of theophylline when added to standard therapies in patients hospitalized for asthma exacerbation.

Study design
PubMed search of the English literature using the key terms theophylline (and aminophylline), asthma exacerbation, and treatment of patients hospitalized for asthma.

Study population /Sample size
Pediatric patients: Yung's study (72) of 163 patients and Ream's study (53) of 47 patients. Both studies are reviewed elsewhere in this document.

Results

Recruitment/ Number analysed
Unclear selection of studies.

Conclusion
Theophylline may improve asthma symptoms, FEV1 and prevent intubation in critically ill children with severe asthma exacerbations that fail to respond to adequate high-dose routine therapy (inhaled beta2-agonists, systemic corticosteroid and inhaled ipratropium) but it should be used only by clinicians who are prepared to order appropriate doses, monitor serum concentrations, and assess factors that modify clearance of this high-risk drug.

Assessor's comments:
Not a systematic review.
The value of theophylline is limited and in children hospitalized with severe asthma exacerbations restricted to non-responders of high-dose standard therapy (inhaled beta2-agonists, systemic corticosteroid and inhaled ipratropium).

Murphy et al 1991 (43)
Title: *Treatment of asthma in children.*
Description
Review of the epidemiology, etiology and pathophysiology, clinical presentation and diagnosis and drug therapy of asthma in children.

Conclusion
The authors state that "in recent years the use of theophylline in both short- and long-term management of asthma has come into question.

Assessor's comments:
Rather old review. Conclusions obsolete after the emergence of inhaled beta2agonists. Summary of age-dependent pharmacokinetics.

Hendeles et al. (23)
Title: *Revised FDA labeling guideline for theophylline oral dosage forms*

Description
The intent of the guideline is to provide a comprehensive package insert required to be followed by all manufactures and distributors that will include all of the information needed to use theophylline safely and effectively.

Conclusion (from the clinical overview)

Paediatrics (PK)
The clearance of THEO is very low in neonates. THEO clearance reaches maximal values by one year of age, remains relatively constant until about 9 years of age and then slowly decreases by approximately 50% to adult values at about age 16. Renal excretion of unchanged THEO in neonates amounts to about 50% of the dose, compared to about 10% in children older than three months and in adults. Careful attention to dosage selection and monitoring of serum THEO concentrations are required in pediatric patients.

Paediatric Use
THEO is safe and effective. The maintenance dose of THEO must be selected with caution in children since the rate of THEO clearance is highly variable across the age range of neonates to adolescents. Due to the immaturity of THEO metabolic pathways in children under the age of one year, particular attention to dosage selection and frequent monitoring of serum THEO concentrations are required when THEO is prescribed to children in this age group.

Assessor's comments:
Paediatric use: Safe and effective, but its use should follow expert guidelines.

MAH 2 conclusion:

1. Theophylline remains a well known and established treatment option with proven effectiveness in childhood asthma and well defined risks, such as adverse events and risk of intoxication with higher doses that exceed the desired plasma levels of 10-20 µg/ml.
2. No new information is available that would alter the status of theophylline as a third-line asthma medication for children and adolescents as recommended in the current guidelines (British Guideline on the Management of Asthma, revised May 2011; German Guidelines for Diagnosis and Treatment of Asthma Patients 2006).
3. MAH 2 has no proposed changes to the SmPC for Solosin®.

3. Discussion
MAH 2 has provided a wide range of published studies regarding the pharmacokinetics, efficacy and safety of theophylline in children.

MAH 2 has not performed any clinical studies on theophylline in the paediatric population and the conclusion is based on the literature search and the latest PSUR that did not reveal any new safety information concerning the use of theophylline in the paediatric population**.**

The literature review shows that the value of theophylline is limited and in children hospitalized with severe asthma exacerbations restricted to non-responders of high-dose standard therapy (inhaled beta2-agonists, systemic corticosteroid and inhaled ipratropium). Theoophylline have a place in therapy in the management of severe acute asthma in children unresponsive to initial treatment.

II. MAH 3 GEBRO PHARMA

II.1 Information on the pharmaceutical formulation used in the clinical study(ies)

MAH refers to the sustained release (SR) theophylline products of the company Gebro Pharma GmbH with the trade names:

Theospirex retard 150 mg – Filmtabletten
Theospirex retard 300 mg – Filmtabletten

Both kinds of tablets have a breaking line. Minimum possible dosing is 75 mg.

II.2 Non-clinical aspects

No non-clinical studies were submitted by the MAH 3.

II.3 Clinical aspects

1. Introduction

The MAH 3 has submitted a short expert overview in addition to a clinical overview by the same author submitted 2009 to the Austrian authorities on the occasion of a national renewal in 2009.
The clinical overview addresses the following issues in regarding treatment with theophylline in children:

- Pharmacokinetics
- Pharmacodynamics
- Clinical use, efficacy of theophylline in children
  - Indications and treatment guidelines
  - Clinical trials in children – ***Zarkovic and Götz 1991 + 1993 + 1995***
  - Dosage in children
- Patients exposure and safety in children and adolescents of Theospirex retard products.

Pharmacokinetics

No phase 1 studies were performed in children. MAH 3 point out that pharmacovigilance over more than 25 years has not revealed any dose dumping or unexpected kinetic behavior of the Theospirex® products.
No bioequivalence studies were performed with any strength of Theospirex in children or adolescents.
Regarding pharmacokinetic parameters in children the MAH 3 refers to the clinical overview of 2009:

- Absorption
  - Not addressed
- Plasma protein binding
  - Not addressed
- Distribution volume, plasma clearance, elimination half-life
  - For the distribution volume a range from 0.3 to 0.7 l/mg was observed, average values were about 0.40 to 0.45 l/kg, both for children and adults.
  - The elimination in children is faster than in adults, however, extremely slow in neonates.
- Metabolism and elimination
  - In neonates, several of the metabolic pathways are underdeveloped resulting in extended half-life time in newborns: approximately 30 hours in newborn and 6 hours in adults.
  - Metabolism of theophylline in foetuses primarily involves methylation to caffeine (Aranda et al., 1979). The plasma half-live in children is about half that of adults (Grygiel et al., 1980)

Pharmacodynamics

MAH 3 refers to a review by Weinberger (68) that says that *"optimal blood levels do not differ between adults and children, however, the pharmacokinetic is*

age dependent and higher dosages per kg bodyweight are needed for children."

MAH 3 points out major discrepancies in the recommended theophylline blood levels. In the Anglo-American countries the recommended blood levels are from 10 ug/ml to 20 ug/ml, but lower in Austria/Germany and Denmark/Sweden.

Indications and treatment guidelines

Current approved indication for the MAH 3 product is

Treatment and prevention of dyspnoea due to narrowing of the airways (bronchoconstriction) in patients with persistent bronchial asthma or moderate to severe chronic obstructive lung disease (e.g. chronic bronchitis and pulmonary emphysema). Medicinal products with extended theophylline release such as Theospirex retard 150/300 mg film-coated tablets are not for the acute treatment of status asthmaticus or the occurrence of acute bronchospasticity.

In

Children and adolescents:
This medicinal product is intended for children from 6 years of age.

(SmPC Theospirex retard, Austria)

National guidelines for the asthma treatment of children (Austria and Germany) recommends theophylline as an option if asthma control is insufficient according to stepwise scheme as illustrated below.

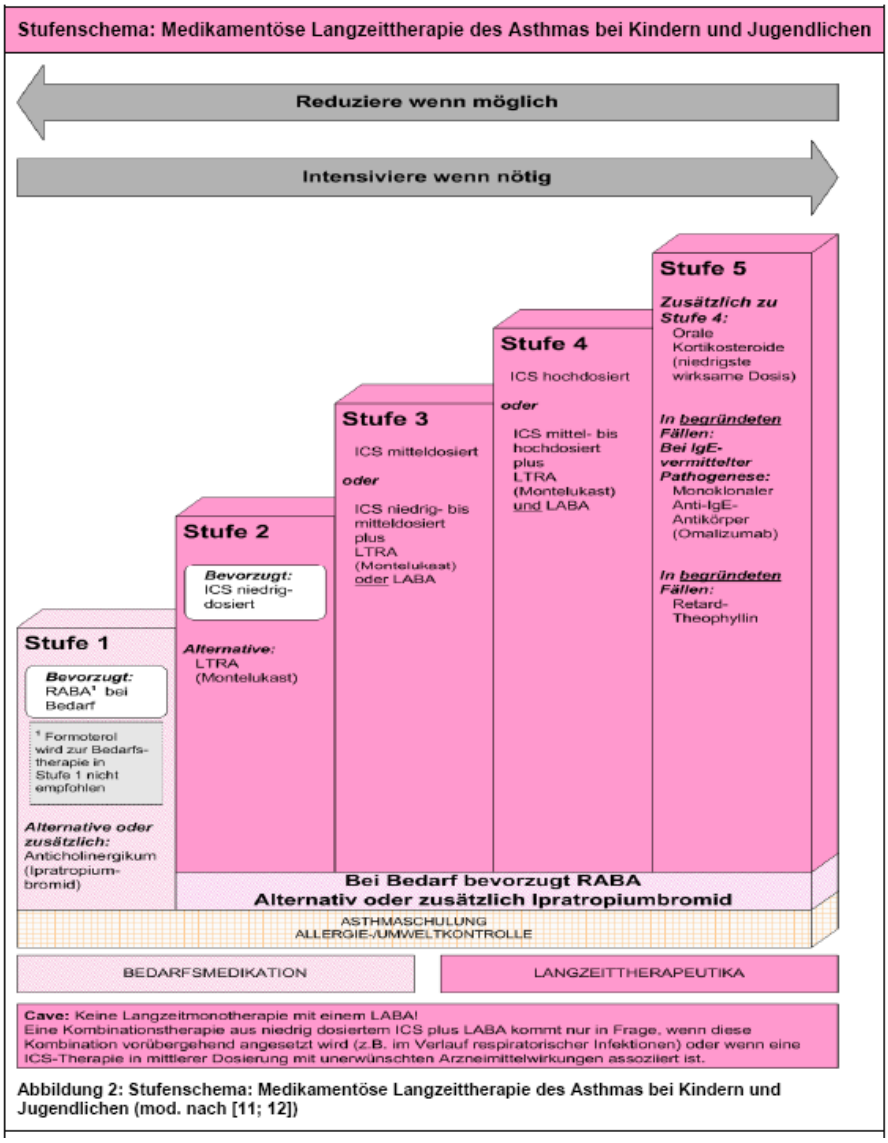


Abbildung 2: Stufenschema: Medikamentöse Langzeittherapie des Asthmas bei Kindern und Jugendlichen (mod. nach [11; 12])

Clinial trials in children

MAH 3 has submitted three clinical studies in children. The studies have been performed on the initiative of investigators, all by the same group (Zarkovic et al). One of the studies are published in German (not indexed in PubMed), the two others are congress summaries.
MAH III has not submitted a literature review.

Zarkovic et al, 1991
Title *[Sustained release theophylline in paediatrics. A comparative study]*

Description
Paper in German including English summary. Small randomized, comparative study of two theophylline preparations.

Methods

Objective(s)

Comparative study of two sustained release preparations of theophylline in children

Study design

Open, randomized, crossover comparative study

Study population /Sample size

Twenty-two children with chronic obstructive lung disease.

Treatments

Theospirix® 150mg “film coated” or Unifyl 200 mg administered with equal doses about 15 mg theophylline/kg. Treatment 3 ½ day each. No wash out period.

Outcomes/endpoints

On day 4 in the morning blood levels were measured (before dosing the other medication of the cross over). On the same days in the morning lung function was evaluated (FEV1, airway resistance, FVC, PEFR).

Statistical Methods

Unclear.

Results

Recruitment/ Number analysed

Blood levels were measured on day 4 and day 7 before administration and also 4, 6 and 8 hours after the morning dose. One patient dropped out, because he was not cooperative. Results of 21 patients were evaluated.

Baseline data

Nine males, mean age 13.44 sd 1.5 and 12 females mean age 9.50 sd 1.83.

Efficacy results

Theospirix® slightly higher blood levels and significantly improved FVC and FEV1, but no difference in PEFR and airway resistance.

Safety results

No adverse events.

Conclusion

The authors conclude that the number of patients is too low and the duration of the treatment is too short to draw any conclusion.

Assessor’s comments:

Slightly better effect of the preparation that also had slightly higher blood levels. No additional information.

Zarkovic et al, 1993
Title: *Medication induced modulation of T-cell subsets in asthmatic children*

Description
Short summary of oral presentation, (copy-pasted from clinical overview).
Study of the expected antiiflammatory effect of theophylline.

In an open study with Theospirex® 150 mg (desired serum levels of theophylline 10 – 15 µg/ml)
in 37 asthmatic children aged 11.9 (sd 4.1) years for 3 months several immunological parameters were evaluated together with respiratory signs and symptoms and laboratory data and compared to 80 and 120 mg disodium-cromoglycinate (DSCG) inhalation. In all patients respiratory parameters improved. IgE was decreased by all treatments but significantly only with DSCG. Under Theophylline B-lymphocyte number increased significantly; an increase was also seen for DSCG, but this was not significant. CD4/CD8 index increased after all treatments but not significantly.
Conclusion: The authors suggest that the effects of these substances in COPD may be due to their possible influence on the process of switching by acting on T-cell subsets and therefore determining B-lymphocyte function reflecting IgE synthesis.

Assessor's comments:
Exceptional study of the pharmacodynamics of theophylline in children with measures of immunological parameters.

Zarkovic et al, 1995
Title: *Theophylline-modulation of bronchial hyper-reactivity (direct and indirect) and T- cell subsets in atopic asthmatic children*

Description
A study of the effect of theophylline of bronchial hyper-reactivity.

Methods
Objective(s)
To study the direct and indirect modulation of bronchial hyperactivity by theophylline

Study design
Open preliminary study.

Study population /Sample size
Twenty-four asthmatic children

Treatments
Theophylline (serum levels 10-15 ug/ml) for three months.

Outcomes/endpoints
Blood samples before and after 3 months of treatment. (Haematological, biochemical, renal function, liver function, inflammatory markers, humoral and cellular immunity.)
Lung function: FEV1 and others.

Statistical Methods
Two-sided t-test and analysis of variance.

Results
Recruitment/ Number analysed
Twenty-four children with asthma.

Baseline data
Twenty males, 4 females, mean age 11.9 ± 4.4 years.

Efficacy results
B-lymphocytes and CD16 (NK cells) were significantly reduced. No significant differences in lung function parameters.

Safety results
Not addressed.

Conclusion
The authors conclude that theophylline influences (reduces) bronchial hyper-responsiveness and suggest further trials in larger patient groups.

Assessor's comments:
Indications that theophylline reduces bronchial hyper-reactivity in children with asthma.

Dosage in children (and adolescents)
MAH 3 has compared the dose recommendations of theophylline in children and adolescents in several EU-countries and finds remarkable differences.

The following table gives an overview of differences concerning theophylline dosages in some EU countries. Obviously the differences are quite remarkable!

	AT Theospirex		FR Euphylline LA 200 mg		PL/HU Theospirex		DE "Mustertext"*		UK Uniphyllin**		DK/SE Theodur**	
Age	bw (kg)	Th. mg/l	bw (kg)	Th.mg/l	bw (kg)	Th.mg/l	bw (kg)	Th.mg/l	Bw (kg)	Th.mg/l	bw (kg)	Th.mg/l
6-9 HU/PL 5-9 DE FR 6-8	20-25	20-24	20-25	10-14# 13-20+	18-30 (HU)	10-17 PL max: 24	20-25	24		18	12-15	13-16
9-12 DE 8-12 PL 10-12	25-40	16	25-40		30-40 (HU)	11-15 PL max: 20	25-40	20		18	20-40	10
FR 9-16			> 25	10-12# 10-16+								
12-16 PL 13-16	40-60	13			40-55 (HU)	8-15 PL max: 18	40-60	18		18?	50	8

* Kind of "class lebelling"
**no age groups given, only bw.
starting dose (FR)
+ usually effective dose (FR)
Th.mg/l= theophylline blood levels (mg/l) recommended

Pateint exposure and safety in children
MAH 3 have had Theospirix® marketed in EU since 1985 and estimate that less than 2 % of the 150 mg tablets are used in children.

	Period	Countries	No of 150 mg tablets
PSUR 1	01.04.1985 – 30.09.1997	AT, PL, HU, DE	19,557,520
PSUR 2	01.July 2001 – 31.March 2003	AT, PL, HU, DE	50,744,800
PSUR 3	01.April 2003 – 31.March 2008	AT, PL, HU	188,668,870
PSUR 4	01.April 2008 – 30.June 2009	AT, PL, HU	55,941,770

MAH 3 has never received any spontaneous reports in PSURS concerning children and adolescents.

MAH 3 conclusion

1. Theophylline seems to have a high level of safety, also in children and adolescents.
2. The use of theophylline is limited in children in concordance with national and international guidelines.
3. Dose recommendations are very different between countries and MAH 3 recommends implementing the lower starting dose, as those recommended in Denmark or Sweden.
4. MAH 3 has not provided suggestions for specific SmPC changes.

3. Discussion

MAH III has provided three unpublished studies of theophylline in children. The studies do not add further to the knowledge of treatment with theophylline in children, but one of them is a rare study of the pharmacodynamics in children with measures of immunological parameters.
Pharmacovigilance over more than 25 years has not revealed any dose dumping or unexpected kinetic behavior of the theophylline in children.
Dose recommendations are very different between countries and MAH 3 recommends implementing the lower starting dose, as those recommended in Denmark or Sweden.

III. MAH 4 BIOPHAUSIA/ASTRAZENECA

III.1 Information on the pharmaceutical formulation used in the clinical study(ies)

Theo-Dur is available in 200mg and 300mg prolonged release tablets and is approved nationally in Sweden, Norway and Denmark.

III.2 Non-clinical aspects

No non-clinical studies have been submitted.

III.3 Clinical aspects

1. Introduction

MAH 4 has made a literature review on pediatric use of theophylline.
Totally 13 studies and two case reports have been submitted.
Three of the studies (Kjellman, Radwan, Eslami) were also submitted by another MAH and only Conclusion and Assessor's comments are repeated.

2. Clinical study(ies)

Kjellman et al (35) – previously assessed in this document
Title: ***Theophylline pharmacokinetics in children, comparing sustained release spheres (Theo-Dur sprinkle) with elixir***

Conclusion
Theo-Dur sprinkle showed satisfactory sustained release properties but the study confirmed the need for individually tailored dosage of theophylline based on monitoring of symptoms and serum concentrations..

Assessors comment:
Satisfactory sustained release properties and possible b.i.d administration of Theo-Dur sprinkle, but again substantial inter- individual variation and need for monitoring of serum concentrations.

Lonnerholm et al 1981 (38)
Title: ***Combined treatment with sustained-release theophylline and beta2-adrenoceptor-stimulating agents in chronic childhood asthma***

Description
Cross-over trial of the effect of theophylline in children with chronic asthma treated with beta2 stimulants.

Methods
Objective(s)
The effect of adding theophylline to treatment with a beta2stimulant in children with chronic asthma.

Study design
Double-blind, randomized, cross over trial.

Study population /Sample size
Eighteen children with moderate to severe chronic allergy asthma.

Treatments
Placebo or theophylline with theophylline dose titrated before the first treatment period to plasma concentration of 7-15 ug/ml.

Outcomes/endpoints
Self-reported symptom scores.FEV1 and PEFR (peak expiratory flow rate), co medication, side effects. Plasma concentrations. Only data from day 4-14 were used (ptt in steady state).

Statistical Methods
Student's t-test. Wilcoxon signed rank test for the preference of treatments.

Results
Recruitment/ Number analysed
Seventeen of the 18 patients completed the study.

Baseline data
Twelve boys and six girls with a median age of 11 years (range 7-14)

Efficacy results
Five patients in the placebo group required emergency room treatment compared to none in the treatment group. Statistically improvement in two of five symptom scores and one of the four daily measures of FEV1. Fourteen preferred theophylline, three expressed no preference, none preferred placebo.

Safety results
Few and mild side effects with no difference between treatment and placebo.

Conclusion
The authors conclude that adding submaximal doses of sustained-release theophylline to treatment with a beta2 stimulant gave further relief of asthmatic symptoms without appreciable side effects, suggesting that the drug combination has a favorable therapeutic index.

Assessors comment:
The children in the study were not treated with inhaled corticosteroids that today is standard treatment. The results therefore are not relevant to clinical practice today.

Igarashi et al 2009 (27)
Title: Effect of gender on theophylline clearance in the asthmatic acute phase in Japanese pediatric patients

Description
Retrospective study to investigate if gender affects the theophylline clearance.

Methods
Objective(s)
To investigate the effect of gender on theophylline clearance in the asthmatic acute phase in Japanese children under 10 years-old.

Study design
Retrospective investigation with review of medical records.

Study population /Sample size
Patients who had correctly received intravenous constant-rate infusion of aminophylline and then had their steady state theophylline concentration measured.

Treatments
Intravenous constant-rate infusion of aminophylline

Outcomes/endpoints
The theophylline clearance (ml/h/kg) of each patient was calculated from the formula, clearance=10^3*R/Css. Where R is the constant infusion rate of the dose of theophylline (mg/h/kg) and Css is the steady state concentration of theophylline (m g/ml).

Statistical Methods
Unpaired Student's *t*-test or Welch's *t*-test. Demographic characteristics of the patients were analyzed by chi-square test or unpaired *t*-test. No correction for mass significance.

Results
Recruitment/ Number analysed
In total, 96 pediatric patients in the asthmatic acute phase.

Baseline data
Sixty-three males and 33 females ranging in age from 0.5 to 8 years and in weight from 6.3 to 36.8 kg.

Efficacy results

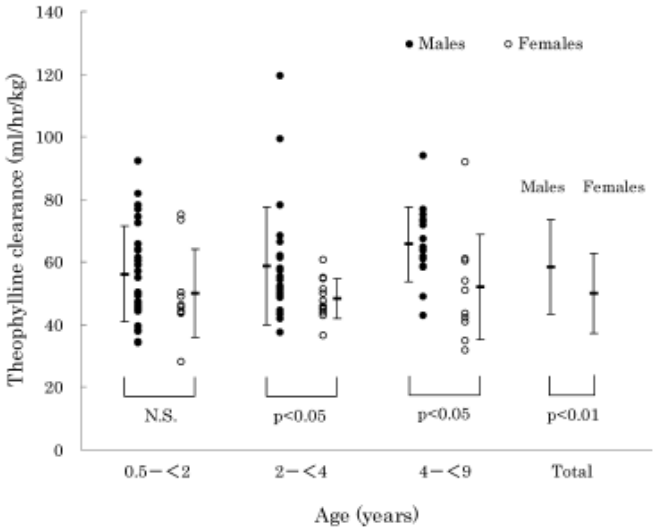


Fig. 1. Effect of Gender on Theophylline Clearance in Different Age Groups

Each point represents the value of theophylline clearance from each patient. Bars represent the mean±S.D.

The clearance for the female patients were similar among the three age groups studied.

Safety results
Not addressed.

Conclusion
The authors argue that they have shown a significant lower theophylline clearance in for Japanese girls aged 2 to 8 years compared to boys in the acute asthmatic phase.

Assessors comment:
Questionable conclusion of difference in theophylline clearance in girls and boys with no clinical importance.

Kumar et al. 2004 (37)
Title: *Acute respiratory infection with CNS excitation symptoms--consider theophylline over-dosage*

Description
Descriptive study of the possibility of theophylline overdose in infants admitted with acute respiratory infection and CNS excitation.

Methods
Objective(s)
To find the cause of CNS excitation symptoms in children presenting with acute respiratory infection.

Study design
Descriptive study

Study population /Sample size
Ten children admitted in the study period.

Treatments
Not relevant

Outcomes/endpoints
The age, sex, clinical manifestations, concurrent medical illness and medications. Serum theophylline level at admission time, in addition to serum electrolytes, serum calcium, CSF analysis and chest radiograph.

Statistical Methods
None

Results
Recruitment/ Number analysed
Ten children, six cases had evidence of theophylline over dosage.

Baseline data
Of the six: five male and one female. Age 45-90 days.

Efficacy results
Not applicable.

Safety results
Theophylline > 15 ug/ml in the six children. The most common manifestations were irritability (100%), tremors (83.3%), seizures (66.6%), and vomiting (50%). Tachycardia

and tachypnea were seen in all children. All these 6 children had received theophylline preparations by local practitioners before admission.

Conclusion
The authors highlight the possibility of theophylline over dosage in young infants treated for acute respiratory infection presenting with CNS excitation symptoms and advise to ensure appropriate dosage and frequency when administering theophylline preparations to young infants with respiratory infection.

Assessors comment:
Stress the point of the narrow therapeutic index of theophylline, the CNS manifestations as signs of theophylline toxicity and the risk of decreased clearance in febrile patients. The study in itself has low scientific value. Fever is reported in section 4.4. in all the submitted SPCs.

Haruyama et al, 2008 (22)
Title: ***The relationship between drug treatment and the clinical characteristics of febrile seizures***

Description
Descriptive study that identifies theophylline as a risk factor for prolonged convulsions in children with fever seizures.

Methods
Objective(s)
To investigate the relationship between the clinical characteristics of febrile seizures and the use of medications (i.a. theophylline).

Study design
Descriptive study

Study population /Sample size
Two hundred and sixty-five children aged 6 months to 6 years treated at our emergency room due to febrile seizures.

Treatments
Nineteen of the 265 patients took theophylline at admission.

Outcomes/endpoints
The number, type, and duration of convulsions.

Statistical Methods
The Mann-Whitney non-parametric test.

Results
Recruitment/ Number analysed
Nineteen of the 265 patients.

Baseline data
No addressed

Efficacy results
Not applicable.

Safety results
The duration of convulsions was longer among children who took theophylline and antihistamines than among children who did not take these medications.

Table 2. Relationship between drug treatment and seizure duration

Drug treatment	*n*	Duration (min)
No drugs	125	4.8±6.5*
Antihistamine only	52	4.5±5.8
Theophylline only	8	9.1±11.3
Theophylline and antihistamine	11	7.0±6.1
Theophylline and mequitazine	5	3.8±3.6
Theophylline and antihistamine other than mequitazine	6	9.7±6.8*

*: $P<0.05$, comparison between childrn who took no drug and those who took theophylline and an antihistamine other than mequitazine.

Conclusion
Theophylline should not be used in febrile children, particularly infants.

Assessors comment:
Theophylline clearance may be decreased by fever (and other conditions) with risk of over dose/toxicity. This is reported in section 4.4 in all the submitted SPC's, in UptoDate and Micromedex©.

Radwan et al 2010 - previously assessed in this document
Title: *Effect of different monotherapies on serum nitric oxide and pulmonary functions in children with mild persistent asthma.*

Conclusion
The authors state that inhaled corticosteroid seems to yield the best response, but further larger studies are needed to validate the findings. The authors argue that mild persistent asthma in children should be treated with a controller medication, and that theophylline may be a good cost-benefit alternative for low socioeconomic groups of patients.

Assessor's comments:
Small open study. Theophylline may be a good cost-benefit alternative for low socioeconomic groups of patients, but this raise safety issues in terms of need for individual dosing based on serum measurements.

Korematsu et al, 2010 (36)
Title: "*The indication and effectiveness of low-dose erythromycin therapy in pediatric patients with bronchial asthma*"

Description
The effect of erythromycin on theophylline metabolism.

Methods

Objective(s)

To evaluate the effect of low dose erythromycin on serum chemokines (i.a. IL8 and VEGF) and on theophylline metabolism.

Study design

The chemokine study is a matched case-control study, but the theophylline study a descriptive study of four patients.

Study population /Sample size

Fifty-five pediatric patients with bronchial asthma and 10 age-matched non-allergic non-febrile disease controls. Only four patients with severe-type asthma were examined. Theophylline metabolism was calculated in three patients.

Treatments

Low-dose EM (10 mg/kg/day divided twice) was added on their current medications such as inhaled steroid, leukotriene receptor antagonist and theophylline for four severe-type patients.

Outcomes/endpoints

Before and 6 months after the co-administration of low-dose EM and theophylline, theophylline clearance, half-time and AUC (area under the curve) were calculated based on 4–6 samples of the serum theophylline concentrations such as trough levels, and 4 and 6 h after administration.

Statistical Methods

The daily peak-trough fluctuation rate of theophylline level was calculated using the formula; (Cmax) Cmin)/Cmin. A statistical examination was performed using the Kruskal–Wallis test and the Wilcoxon signed rank test.

Results

Recruitment/ Number analysed

Three of the four patients of the original 55.

Baseline data

Age 2(F), 7(M) and 9(M) years old.

Efficacy results

After the co-administration of erythromycin and theophylline for three of four severe-type patients, the theophylline clearance decreased from 0.093 ± 0.001 to 0.062 ± 0.013 l/kg/h, and the half-time increased from 6.3 ± 1.0 to 9.9 ± 3.3 h and the AUC (area under the curve) increased from 168.7 ± 74.4 to 261.7 ± 149.5 mg/CL · Wt. Such an altered theophylline metabolism resulted in a decreased daily peak trough fluctuation rate of the serum theophylline concentration; (Cmax) Cmin)/Cmin, from 1.3 ± 0.5 to 0.5 ± 0.3

Safety results

Not addressed.

Conclusion

Unexpected discovery that a low dose erythromycin in children with severe asthma decreased the daily fluctuations of theophylline.

Assessors comment:
The study confirms the drug interaction between erythromycin and theophylline, also in children. The clinical value of the coincidental observed "beneficial" effect with a decreased peak through fluctuation rate of the serum theophylline concentration is questionable.

Suzuki et al, 2009 (62)
Title: "*Estimating pediatric doses of drugs metabolized by cytochrome P450 (CYP) isozymes, based on physiological liver development and serum protein levels"*

Description
Methodological study that compares two different methods for estimating pediatric doses of drugs metabolized by CYP enzymes using data from the literature.

Methods
Objective(s)
To compare two different methods to estimate pediatric doses of drugs metabolized by cytochrome P450 (CYP) isozymes.

Study design
Methodological study.

Study population /Sample size
Reference to previous study by the authors. Otherwise published data of Japanese children up to 15 years.

Treatments

Outcomes/endpoints
New method of pediatric dose estimation that incorporates the influence of the physiological/biochemical development (Unbound fraction, serum protein level, liver volume, CYP activity).
Comparator: pediatric dose calculated from child/adult body surface area ratio .
Reference: predetermined doses

Statistical Methods
Relative root mean squared prediction error (Relative RMSE)

Results
For all drugs, including theophylline, the new method was more accurate with the predetermined dose as reference.

Conclusion
Dose estimation based on body surface area is inadequate, especially for infants and neonates. Activity of CYP1A2 is not fully developed in childhood, and a dosing estimation method that incorporates CYP activity seems to be superior the body surface area method.

Assessors comment:
Methodologically important study that addresses the complexity of pediatric dosing. For substrates with substantial metabolism by CYP enzymes like theophylline the pediatric dose should optimally reflect the CYP activity that develops during childhood.

Eslami et al 2009. (17) Previously assessed in this document
Title: *Theophylline for prevention of kidney dysfunction in neonates with severe asphyxia*

Assessor's comments:
Prophylactic theophylline is not standard treatment in neonates to prevent renal dysfunction, and the results of this study not convincing

Alvaro et al 2012 (1)

Title: *CO(2) inhalation as a treatment for apnea of prematurity: a randomized double-blind controlled trial*

Description
Efficacy of theophylline for apnea of prematurity compared to C02.

Methods
Objective(s)
To compare the effect of prolonged inhalation of a low concentration of CO2 with theophylline for the treatment of apnea of prematurity.

Study design
Prospective, randomized, double-blind controlled trial. Stratification by gestational age.

Study population /Sample size
Trial of 87 preterm infants with apnea of prematurity (27-32 weeks' gestational age)

Treatments
Either theophylline plus 0.5 L/min of room air via nasal prongs or placebo plus 0.5 L/min with CO2 (about 1% inhaled) by nasal prongs for 3 days.

Outcomes/endpoints
The primary endpoint of the study was the decrease in total apnea time(duration of all apneic pauses ≥ 5seconds).The secondary endpoints were the decrease in the rate of long apneas (≥20 seconds) and the incidence of short-term side effects.

Statistical Methods
ANOVA, Kruskal-Wallis ANOVA, and median test were used to test the differences within and between both treatment groups.

Results
Recruitment/ Number analysed
Of 191 eligible infants, 147 were asked to participate, and 87 infants were enrolled after parents consent. Seven infants in the CO2 group (18%) but none in the theophylline group, failed treatment and were withdrawn from the study.

Baseline data		Theo:	C02
Infants at birth:	Birth weight, mean g (SD)	1460 (324)	1422 (305)
	Gestational age, mean wk (SD)	29.8 (1.6)	29.6 (1.5)
	Apgar score, median (range) 1 min	7 (1-9)	5 (1-8)
	5 min	8 (6-9)	8 (5-9)
	Male, n (%)	17 (41)	18 (47)

Efficacy results

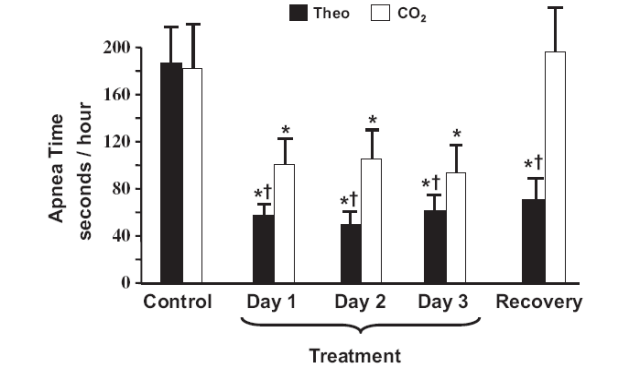


Figure 2. Primary endpoint: Although both treatments were effective in reducing apnea time, theophylline was more effective than CO_2. *$P \leq .05$ compared with control; †$P < .05$ compared with CO_2.

Safety results
The number of episodes of tachypnea, tachycardia, moderate to severe episodes of emesis, and jitteriness significantly increased only during theophylline treatment (P < .001).

Conclusion
Theophylline was more effective in reducing the number and severity of apneas than C02 alone.

Assessors comment:
Theophylline is effective in the treatment of apnea of prematurity, but caffeine is used in today clinical practice because of more predictable kinetics and fewer adverse reactions.

Deters et al, 2009 (13)
Title: *Iatrogenic intravenous medication errors reported to the GIZ-Nord Poisons Center Gottingen*

Description
Analysis of iatrogenic, intravenous medication errors reported to a poison center.

Methods
Objective(s)
To analyze iatrogenic intravenous medication errors (IIME) reported to a poison center.

Study design
Retrospective analysis of IIME

Study population /Sample size
In total, 265 IIME registered in the study period 1997-2006.

Outcomes/endpoints
IIME

Results
Three of the fourteen IIMEs with severe outcome involved theophylline, one of these involved a child, a 3-year-old boy that received 300 mg theophylline iv after general anesthesia.

Conclusion
Dosing error of theophylline was implicated multiple times with severe or fatal outcome.

Assessors comment:
The study confirms that theophylline has a narrow therapeutic range and the examples show that erroneous IV administration of even a therapeutic dose twice can result in severe theophylline overdose. The use of intravenous administration of theophylline should be well argued.

Imai et al, 2012 (28)
Title: *Influences of pyrexia and age on theophylline clearance in young children with asthma*

Description
Pharmacokinetic study that investigates the influence of fever on theophylline clearance.

Methods
Objective(s)
To investigate the pharmacokinetics of theophylline in the present of pyrexia (fever).

Study design
Pharmacokinetic study.

Study population /Sample size
Fifty hospitalized children with asthmatic bronchitis and bronchial asthma treated with a iv-theophylline infusion. The patients were divided into two groups based on body temperature: a pyrexia group (≥ 38°G) and a nonpyrexia group < 38°C).

Treatments
Theophylline dose 0,4 mg/kg/hr in ≤ 6 months age group and 0,8 mg/kg/hr in the oldest age group 2 – 3 years.

Outcomes/endpoints
Theophylline clearance calculated from Css, weight and infusion rate.

Statistical Methods
ANOVA and multivariate analysis.

Results
Recruitment/ Number analysed
Data from 50 patients, 25 with fever and 25 without.

Baseline data
Age 3 months to 2.9 years.

Efficacy results
In all age groups, theophylline clearance of the pyrexia group was significantly less than that of the non-pyrexia group ($p < 0.01$), showing that there was a significant pharmacokinetic difference in theophylline clearance between the groups.

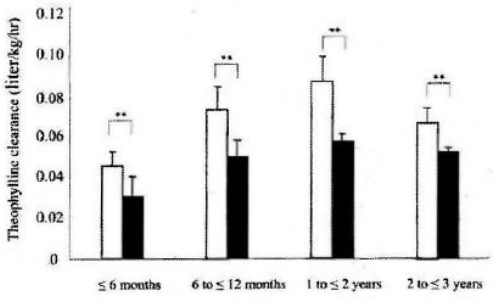


Fig. 2. Effect of pyrexia on theophylline clearance by age
Each value represents mean ± S.D.
■: Pyrexia group; □: Non-pyrexia group.
**p < 0.01 compared with the non-pyrexia group.

Safety results
Due to great individual variation still dosage should be based on TDM.

Conclusion
This study showed that the presence of pyrexia decreases theophylline clearance, and that it affects theophylline clearance in an age-dependent manner.

Assessors comment:
Fever may cause decreased theophylline clearance as mentioned earlier and in SPCs.

Skouroliakou et al, 2009 (59)
Title: *Caffeine versus theophylline for apnea of prematurity: a randomised controlled trial*

Description
Methods
Objective(s)
To compare standard doses of theophylline and caffeine for apnea of prematurity in terms of apnea frequency and assess the need for therapeutic drug monitoring.

Study design
Open-label, randomized, controlled trial.

Study population /Sample size
Seventy neonates < 33 weeks of gestation, breathing spontaneously

Treatments
Randomly assigned to receive either theophylline (4,8 mg/kg loading dose, maintenance dose 2 mg/kg/12 hr) or caffeine (20 mg/kg loading dose, maintenance dose 5 mg/kg) for treatment or prevention of apnea.
Treatment (8 theophylline/10 caffeine), prevention (29 theophylline/23 caffeine).

Outcomes/endpoint
Primary outcome the difference in apnea frequency between the groups.

Statistical Methods
Wilcoxon signed ranks test.

Results
Recruitment/ Number analysed
Of 276 infant screened for eligibility, 89 were candidates, and the parents of 78 gave consent. Eight were excluded after randomization.

Baseline data

	Theophylline	Caffeine
Number of patients	37	33
Gestational age (weeks)	30,4	31,5

Efficacy results
No sustained benefit of caffeine over theophylline beyond the first week of therapy.

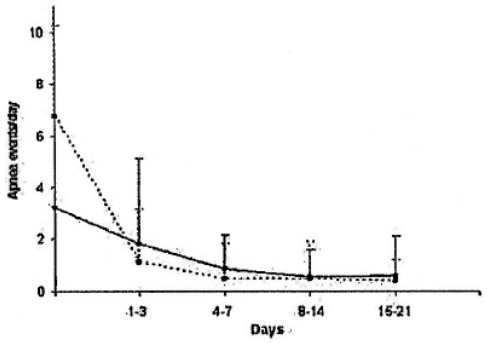


Fig. 3 Mean (±SD) apnea events/day in all infants receiving theophylline (continuous line) or caffeine (broken line) for apnea of prematurity.

Safety results
Plasma concentrations remained stable. Irritability in two patients in the theophyliine group,and one in the caffeine group.

Conclusion
The authors conclude that caffeine has an advantage over theophylline in the first week of therapy, and that standard regimes do not seem to require routine concentration monitoring.

Assessors comment:
Caffeine seems to be preferred over theophylline in the treatment of apnea in preterm infants.

MAH 4 has also submitted two case studies:

1.
Nobutoki et al, 2008 (47)

Title: ***[A 5-year-old boy with nonconvulsive status epilepticus induced by theophylline treatment]***

Article in Japanese with English summary.
A normally developed 5-year-old boy with no history of convulsive disorder resented with a generalized tonic-clonic convulsion diagnosed as nonconvulsive status epilepticus (NCSE) on the second day of oral theophylline therapy. The serum theophylline concentration was 19.7 microg/mL.
Conclusion: Unconsciousness in a child treated with theophylline could be NCSE - an adverse reaction to theophylline

2.
Tesfaye et al, 2008 (64)

Title: [Hypokalaemia in a suicide attempt of an adolescent girl]

Article in Czech with English summary.
A female teenager developed severe hypokalaemia (1,8 mmol/L)following oral theophylline overdose in a suicide attempt. Peak theophylline concentration (68 mg/L).

MAH 4 conclusion:
Based on the review of the literature MAH 4 has made a list of proposals for a revision of the national SmPCs of Theo-Dur in regard to use in children.

Section 4.1:
New indications:
- Kidney dysfunction in neonatal asphyxia
- Apnea of prematurity

Section 4.2:
Dose calculations:
- Update based on new PK data that include free fraction of drug in plasma, serum protein level, liver volume and CYP activity
- Gender effect to be considered
- Effect of pyrexia on theophylline clearance should be considered for children

Section 4.4
Special precaution:
- Administering theophylline preparations to young infants with respiratory infection.
- H1 antagonists and theophylline should not be co-administered to patients with febrile seizures and epilepsy.

Section 4.5
Interactions:
- The drug combination theophylline and beta2stimulants has a favorable therapeutic index.

- The known interaction between erythromycin and theophylline could have a beneficial effect.

3. Discussion

MAH 4 has not provided unpublished studies of theophylline in children.
Theophylline is effective in the treatment of apnea of prematurity, but caffeine is used in today clinical practice because of more predictable kinetics and fewer adverse reactions.

IV. MAH 5 NYCOMED

IV.1 Information on the pharmaceutical formulation used in the clinical study(ies)

MAH 5 has both an intravenous and sustained release oral formulation on the European marked.
The formulation used in the clinical studies is Theophylline Retard 250 mg capsules.

IV.2 Non-clinical aspects

No non-clinical studies were submitted by MAH 5.

IV.3 Clinical aspects

1. Introduction
MAH 5 has submitted a short clinical expert statement with referral to Company Core Data Sheet submitted with PSUR from 2008.
MAH 5 has also submitted four study reports, which MAH 5 consider "*add to the substantial data surrounding the efficacy and safety profile of Theophylline in the pediatric population"*.

Additionally MAH 5 has referred to 11 studies/papers that will be assessed individually.

2. Clinical study(ies)

Synopsis - Study Report Theophylline 84-83, 1983
Title: Theophylline retard (250 mg). Clinical and kinetic findings.

Methods
Objective(s)
To ascertain the clinical effect tolerability and steady state concentration of theophylline.

Study design
Pharmacokinetic study

Study population /Sample size
Eleven young patients with bronchial asthma.

Treatments
Theophylline retard 3 x 250 mg for 15 days.

Outcomes/endpoints
Pulmonary function parameters, blood pressure, laboratory values, serum theophylline concentrations, adverse reactions.

Statistical Methods
Not addressed

Results
Recruitment/ Number analysed
Data from eleven patients

Baseline data
Age 14-16 years, body weight 48-78 kg.

Efficacy results
Negligible changes in pulmonary function. Only FEV1 was significantly improved at treatment day 11 compared to baseline.
Marked inter-individual fluctuations in serum theophylline concentrations and large intra-individual spread. Only five of eleven had serum theophylline concentrations within the therapeutic range (8-20 mg/L).

Safety results
No adverse reactions.

Conclusion
There is a marked inter- and intra-individual variation in regard to the pharmacokinetics of theophylline. This stress the need for invidual dosing based on serum theophylline concentration levels measures. Therapeutic window 8 – 20 mg/L.Dosing three times daily not in line with company recommandations

Assessors comment:
Marked inter- and intra individual variation of theophylline concentrations in adolescents, also with dosing three times daily.

Synopsis - Study Report Theophylline 271-87, 1987
Title: steady state pharmacokinetics and pharmacodynamics of theophylline, in asthmatic children of 9-13 years, after unequal twice-daily dosing of the oral sustained-release formulation BY158K (theophylline)

Methods
Objective(s)
To evaluate steady state PK of theophylline and its metabolites after unequal twice-daily dosing in fast metabolising asthmatics and effect on non-bronchial hyper reactivity.

Study design
Open label under steady state conditions.

Study population /Sample size
Nineteen patients with bronchial asthma.

Treatments
Unequal dosing: theophylline 200 mg capsule in the morning and 2x200 mg in the evening. Four days active treatment.

Outcomes/endpoints
Average steady-state concentrations and peak-trough characteristics. Lung function parameters.

Statistical Methods
Comparisons by means of Wilcoxon-Pratt test.

Results
Recruitment/ Number analysed
Nineteen patients, no withdrawals or drop outs. Data reported for 16 patients.

Baseline data
Four females and fifteen males. Median (range) age: 10.9 (9.1-13.8) years, weight 35 (27-44) kg.

Efficacy results
Steady state concentrations (mean ± SD): Cmin 6.8 ±2.1 mg/L , Cmax 14.5 ±4.8 mg/L, Cave 10.5 ±2.9 mg/L.Peak trough fluctuations 72 ±21%. Lung function improved in 10 of 17, unchanged in 2 and deteriorated in 5.

Safety results
Six patients experienced typical theophylline side effects necessitation dose reduction in three.

Conclusion
Unequal dosing well suited for children with fast metabolism.

Assessors comment:
Unequal (1/3 + 2/3) dosing maybe better in children with faster metabolism.
High rate of adverse events and negligible effect.

Synopsis - Study Report Theophylline 13-89, 1989
Title: Uncontrolled study of serum theophylline concentrations and lung function parameters in 18 children with bronchial asthma between 5 and 9 years of age after four days's administration of 450 mg theophylline per day.

Methods
Study design
Uncontrolled under steady state conditions.

Study population /Sample size
18 children with bronchial asthma

Treatments
Fixed dose of theophylline 150 mg at 0800 hours and 300 mg at 1830 hours.

Outcomes/endpoints
Serum theophylline concentrations, pharmacokinetic parameters, lung function values.

Statistical Methods
Comparisons by means of Wilcoxon-Pratt test.

Results
Recruitment/ Number analysed
Eighteen patients

Baseline data
Median (range) age 7 (5-9) years, weight 26 (20-33) kg,

Efficacy results
Only significant improvement in lung function was 10 % in peak expiratory flow. It is stated in the report that “previously shown excellent pharmacokinetic properties and good tolerance” were confirmed, but there is no data provided.

Safety results

Conclusion
Unequal dosing well suited for children. Variation in individual response to therapy.

Assessors comment:
Limited data. Small, clinical insignificant effect.

Synopsis - Study Report Theophylline 214-92, 1993
Title: Efficacy of BY158K (theophylline) vs terbutaline on the oscillatory resistance in children aged 2 to 5 years suffering from bronchial asthma.

Methods
Objective(s)
To study the efficacy of theophylline vs terbutaline on the airway resistance measured by polyfrequent oscillatory technique.

Study design
Randomized, open labe, parallel group.

Study population /Sample size
Thirty-six patients with bronchial asthma.

Treatments
Four days treatment with either: Theophylline caps 22 mg/kg/day, reduced to 18 mg/kg/day. 1/3 in the morning, 2/3 in the evening or terbutaline 1.25 mg p.o. twice daily.

Outcomes/endpoints
Airway resistance, adverse events.

Statistical Methods
Mann-Whitney two-sided U-test.

Results
Recruitment/ Number analysed
Thirty-six patients recruited, three discontinued because of adverse events.

Baseline data
Age 2-5 years.

Efficacy results
Both treatments effective, no statistically significance between treatments.

Safety results
Adverse events in 9 patients under theophylline treatment due to overdosage, and 2 under terbutaline treatment. Initial dose of theophylline lowered.

Conclusion
Underlines the necessity for careful monitoring of serum peak concentrations to adjustand determine the dose that will provide maximum potential benefit with minimal risk of adverse effects.

Assessors comment:
Dosing 22 mg/kg/day – which is the recommended dosing for children in several SPC's - resulted in substantial overdosage,

Nolan et al, 1982 (48)
Title: *Comparison of the long-term effect of fenoterol hydrobromide and theophylline syrups in pre-school asthmatic children*

Description
Eight week double blind randomized trial with beta2agonist, theophylline and placebo.

Methods
Objective(s)
To compare the clinical effect of fenoterol syrup with theophylline liquid preparation in preschool asthmatic children.

Study design
Four week run-in period on active theophylline followed by three consecutive eight-wwek periods of treatment with either fenoterol, theophylline or placebo. Randomized, double blind, double dummy.

Study population /Sample size
Twenty-two children with moderately severe, non-steroid dependent asthma.

Treatments
Eight weeks with fenoterol, theophylline or placebo syrups. Theophylline dose adjusted to serum concentration ≥ 10 ug/ml. Mean dose 5.5 mg/kg (rang 4.6-6.6) three times a day. Fenoterol 0.1 mg/kg.

Outcomes/endpoints
Diare summaries of symptomsand use of nebulized bronchodilator.

Statistical Methods
Comparison of treatments with ANOVA, verified by Friedman (non-parametric)

Results
Recruitment/ Number analysed
Fifteen patients completed the 28 weeks of the study.

Baseline data

Efficacy results
Significant decrease in cough incidence for both fenoterol and theophylline, and non-significant reduction in wheeze and night time symptoms.

Safety results
Minor side effects.

Conclusion
Significantly reduction in cough for both fenoterol and theophylline

Assessors comment:
Eight week double blind randomized trial of beta2 agonist (fenoterol) and theophylline showed effect of both treatments compared to placebo.

Bender et al, 1992 (6)
Title: *Theophylline-induced behavior change in children. An objective evaluation of parents' perceptions*

Description
Double-blind placebo controlled investigation of theophylline induced behavior changed as percepted by the parents.

Methods
Objective(s)
To evaluate children who take theophylline for the presence of behavioral side effects and to determine whether the beliefs about these side effects held by their parents are supported by their own observations.

Study design
A double-blind, placebo-controlled, randomized, crossover protocol.
After one week washout patients were randomly assigned to theophylline or placebo for one week, and then blindly crossed over.

Study population /Sample size
The subjects were 8- to 12-year-old children with mild to moderate asthma whose parents had observed adverse behavioral side effects while the children were taking theophylline.

Treatments
Theophylline dose reported by parents to cause symptoms, mean 15.0 mg/kg/day.

Outcomes/endpoints
Physiological testing, parent questionnaires, serum theophylline concentrations.

Statistical Methods
Repeated measures analysis of variance.

Results
Recruitment/ Number analysed
Fourty-two children recruited, eleven excluded for non compliance. Data from 31 subjects presented.

Baseline data
Mean age, 10.2 years; 24 boys and seven girls.

Efficacy results
No differences related to treatment could be detected from the parent questionnaires or from six of nine scores of the psychological evaluation of the children. The children, however, made fewer attention errors and showed a mild increase in anxiety and hand tremor of the dominant hand while they were receiving theophylline. All mean changes were small. No significant relationship was found between theophylline concentrations in the serum and degree of change in mood or attention.
Eleven of 42 participants were disqualified for noncompliance during the study.

Safety results

Conclusion
No behavioral side effects could be identified.

Assessors comment:
The behavior changes identified by the parents were not related to theophylline treatment. Note: 11 out of 42 non-compliant!

Katz et al, 1978 (32)
Title: ***The effectiveness of the short- and long-term use of crystallized theophylline in asthmatic children***

Description
Addition of ephedrine to low dose of theophylline in randomized, controlled trial.

Methods
Objective(s)
To determine if a lower dose of theophylline than recommended and/or ephedrine could be effective in asthmatic children requiring daily bronchodilator therapy.

Study design
Randomized, double-blind, crossover design.

Study population /Sample size
Sixyeen children with asthma requiring daily oral bronchodilator preparations.

Treatments
One-week periods of treatment with three seven-day washout periods following each study week. During each treatment week, the patient received one of the following medical regimens every six hours: (1) Crystallized theophylline, 125 mg tablets plus 30 mg ephedrine. (2) Theophylline, 125 mg tablets, and a placebo. (3) Ephedrine, 30 mg, and a placebo. (4) A placebo and a placebo.

Outcomes/endpoints
Daily diary recording day and nighttime symptoms (wheeze, breathlessness, tightness, cough, and attacks). Medications and peak flow.

Statistical Methods
Significance of mean change determined with paired Student's t test., correlation coefficients.

Results
Recruitment/ Number analysed
Sixteen patients.

Baseline data
Eleven boys and five girls with a mean age of 13.0 years (range 9 to 17 years).

Efficacy results
Significant change in FEVI did not occur until serum theophylline concentrations were above 2 ug/ml. Significant improvement in both FEV1 and FEF25_75 are noted at serum T values between 2 to 5 ug/ml.

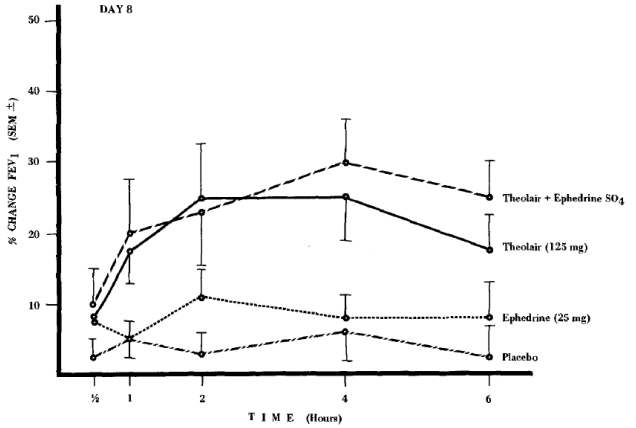


Fig. 2. Day 8: Mean percent change in FEV_1 from baseline in 16 asthmatic children after the ingestion of crystallized theophylline 125 mg; theophylline + 30 mg ephedrine SO_4; 30 mg ephedrine SO_4 + placebo. At 1, 2, and 4 hours the FEV_1 with theophylline and theophylline with ephedrine were significantly ($P < 0.05$) greater than the FEV_1 with ephedrine alone or placebo. Theophylline and theoplylline plus ephedrine were not significantly ($P < 0.05$) more effective than ephedrine or placebo at 6 hours. I represents mean percent change from baseline ± one SEM.

Safety results
None of the patients experienced any significant side effects associated with the use of crystallized theophylline or ephedrine SO4 tablets or placebo.

Conclusion
Addition of ephidrine to the theophylline regimen further improved pulmonary function only on day one and had no effect on the last study day.

Assessors comment:
Comparator/additive drug (ephedrine) obsolete.
Apparent clinical effect at theophylline levels 2 – 5 mg/l. Established therapeutic level 8-10 to 20 mg/l. Theophylline better than placebo.

Bierman et al, 1988 (8)
Title: *Is a uniform round-the-clock theophylline blood level necessary for optimal asthma therapy in the adolescent patient?*

Description
Once daily vs. twice daily theophylline preparation in randomized controlled trial.

Methods
Objective(s)
To compare theophylline preparation administered twice daily with an equivalent daily dose of a another preparation administered once daily at bedtime.

Study design
Ten-week, double-blind, two-way crossover study that compared

Study population /Sample size
Twenty-one patients with nocturnal asthma controlled with sustained release theophylline administered twice daily,

Treatments
Theo-Dur tablets administered twice daily with an equivalent daily dose of Uniphyl tablets administered once daily at bedtime.

Outcomes/endpoints
Daily symptom score card. Cough, chest tightness, wheeze, and difficulty in breathing were scored. Peak expiratory flow rate was recorded three times a day, and night awakenings due to asthma were noted. The patients also recorded the use of all concomitant medications and the time of their use.

Statistical Methods
The data were analyzed by Student's test for repeated measures or by analysis of variance.

Results
Recruitment/ Number analysed
Seventeen of the 21 completed the study.

Baseline data
Of the 21, 13 male and 8 female. Age 12-18 years.

Efficacy results
The mean morning theophylline serum level obtained with Uniphyl tablets was significantly higher than that obtained with Theo-Dur tablets (13.1 versus 9.6 pg/ml, p = 0.02). The mean evening serum level was significantly lower with Uniphyl tablets (6.3 versus 10.1 pg/ml, p = 0.003). Despite these differences in serum concentrations, pulmonary function test values were nearly identical for the two preparations, as was the supplemental use of aerosol bronchodilators.

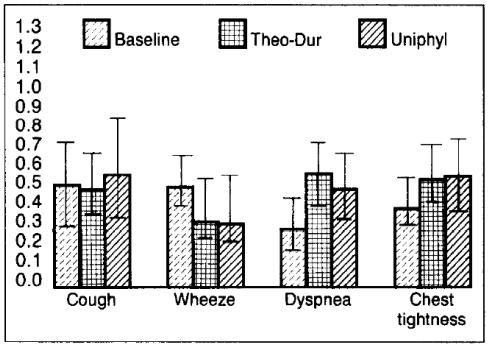


Figure 3. Evening symptom scores (mean ± SEM). 0 = not present; 1 = mild; 2 = moderate; 3 = severe).

Safety results

Conclusion
Nocturnal asthma well controlled with a once-daily theophylline preparation.

Assessors comment:
Low efficacy of both preparations. Once daily administration seems to be non-inferior. Theophylline better than placebo.

Pedersen et al, 1985 (50)
Title: ***Treatment of nocturnal asthma in children with a single dose of sustained-release theophylline taken after supper***

Description
Theophyllin vs. placebo for nocturnal asthma in RCT.

Methods
Objective(s)
To evaluate whether a single dose of sustained release theophylline taken after supper is effective in controlling nocturnal wheezing in children and in maintaining therapeutic serum levels throughout the night.

Study design
Placebo-controlled double-blind cross-over study of 2 x 3 weeks duration.

Study population /Sample size
Twenty-four children with stable asthma.

Treatments
Theophylline or placebo for the first three weeks and then cross-over. Single dose sustained release theophylline, dose most close to 15 mg/kg taken after supper. Mean dose 12.9 mg/kg (range 10.9-15.0 mg/kg)

Outcomes/endpoints
Peak expiratory flow before bedtime and in the morning and every time the child woke up during the night due to asthma symptoms. FEV1, advere events, acute attacks of wheeze, need for bronchodilators.

Statistical Methods
Two-sample t-test.

Results
Recruitment/ Number analysed
All twenty-four completed the study.

Baseline data
Seventeen boys and seven girls. Age 6-15 years, mean 9.2 years.

Efficacy results
Morning peak flow significantly higher during theophylline treatment than placebo. Significant reduction in number and severity of during the night with theophylline.

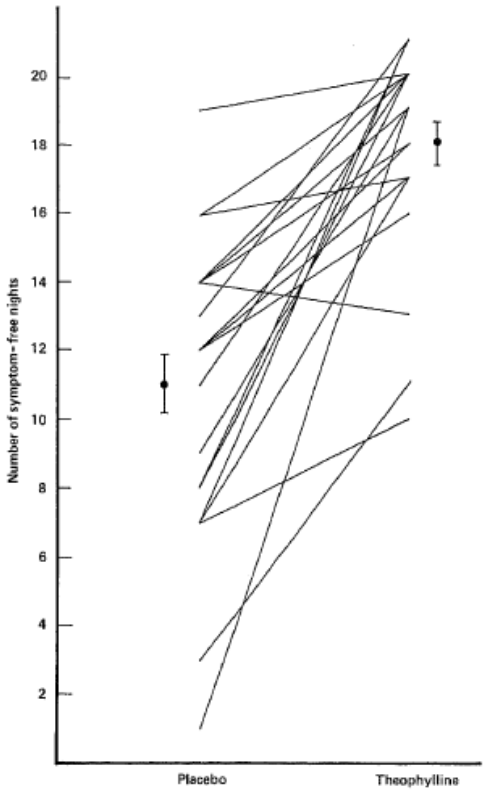


Fig. 1. Individual number of symptom-free nights during the two treatment periods. • indicates group mean value ± s.e.m.

Safety results
Few side-effects.

Conclusion
The authorS conlude that a single dose sustained release theophylline is an effective treatment of nocturnal asthma in children.

Assessors comment:
Theophylline better than placebo. Seventeen of 24 could guess thattheophylline was administrated, the study therefore not truly “double- blind”.

Magnussen et al, 1988 (40)
Title: *Methylxanthines inhibit exercise-induced bronchoconstriction at low serum theophylline concentration and in a dose-dependent fashion*

Description

Assessors comment:
Protective effect of theophylline on exercise induced bronchoconstriction.
The mean age of the eleven patients is 22.3 years (range 16-33 years). The study is irrelevant to the work sharing of pediatric use of theophylline.

Nassif et al, 1981 (44)
Title: *The value of maintenance theophylline in steroid-dependent asthma*

Description
Add-on treatment with theophylline in steroid-dependent children.

Methods
Objective(s)
To investigate the value of long term treatment with theophylline in steroid dependent asthma.

Study design
Placebo-controlled, randomized, double-blind trial. Average follow-up 2 ½ years.

Study population /Sample size
Thirty-three children with steroid-dependent asthma.

Treatments
Twenty-two patients received inhaled corticosteroid (mean dose 533 ug/day) and eleven received oral prednisolone 20-50 mg every morning. Theophylline dose (sustained release preparation twice or three times a day), established to maintain serum concentration 10-20 ug/ml.

Outcomes/endpoints
Nocturnal symptoms recorded on a diary form, use of inhaled beta2agonist co-medication, pulmonary function, and exercise stress test.

Statistical Methods
Paired t-test.

Results
Recruitment/ Number analysed
Al patients completed the study.

Baseline data
Age 7-19 years.

Efficacy results
Patients were free of all symptoms 63 % of the day during treatment compared to 42 % during placebo. Need of beta2agonist doubled and increased need of daily corticosteroid in the placebo group.

Safety results
Adverse effects in six patients after crossover to theophylline, adverse effects mild and declined spontaneously.

Conclusion
Authors conclude that maintenance theophylline can provide clinically important benefit for patients with steroid-dependent asthma.

Assessors comment:
Theophylline improved asthma control in children with severe asthma treated with inhaled or oral glucocortocosteroids. Very long follow-up (> 2 years). Remarkably no loss to follow-up.

Brenner et al, 1988 (11)
Title: *Need for theophylline in severe steroid-requiring asthmatics*

Description
Methods
Objective(s)
To investigate if use theophylline could be eliminated from multi-medication regimen of severe asthmatics.

Study design
Double-blind, cross-over trial of theophylline vs. Placebo.

Study population /Sample size
Five in-patients with a demonstrated requirement for systemic steroids who were taking most other available anti-asthmatic medications in an attempt to reduce need of steroids.

Treatments
Long-acting theophylline to maintain serum concentration between 12 and 16ug/ml.

Outcomes/endpoints
Symptom scores, extra respiratory treatments, increase in steroid dosage, daily spirometri.

Statistical Methods
Student's t-test.

Results
Recruitment/ Number analysed
Data from five patients analyzed.

Baseline data
Age 12-15 years. Four males and one female.

Efficacy results
During the placebo period all five patients required additional dosage of steroids and daily spirometri decreased.

Safety results

Conclusion
The authors conclude that theophylline is beneficial in a subset of severe asthmatics who cannot be controlled with all other medications. The authors stress the point that the lowest possible dose of systemic steroids is paramount because of long-term steroid side effects, which are more serious and harmful than potential short term side effects of theophylline

Assessors comment:
Elimination of theophylline from a multi-medication regimen in children with severe steroid dependent asthma seems to increase the need for steroids.

Wheeler et al, 2005 (70) – assessed previously in this document
Title: *Theophylline versus terbutaline in treating critically ill children with status asthmaticus: a prospective, randomized, controlled trial*

Conclusion
The authors conclude that theophylline, when added to continuous nebulized albuterol therapy and intravenous corticosteroids, is as effective as terbutaline in treating critically ill children with status asthmaticus. The addition of theophylline to baseline therapy is more cost-effective when compared with terbutaline alone or terbutaline and theophylline together. The authors suggest that theophylline should be considered for use early in the management of critically ill asthmatic children.

Assessor's comments:
The study is not placebo-controlled. Only 10 % of eligible patients enrolled in study. Terbutaline is not superior to theophylline as add-on in critically ill children with status asthmaticus.

Henderson-Smart et al, 2010 (25)
Title: *Prophylactic methylxanthine for prevention of apnoea in preterm infants*

Description
Cochrane review of six trials regarding propfylactic treatment of preterm apnea.

Methods
Objective(s)
To determine the effects of prophylactic methylxanthine treatment on the use of intubation and IPPV and other clinically important side effects in preterm infants being weaned from IPPV and in whom endotracheal extubation is planned.

Study design
Cochrane review

Study population /Sample size
Preterm or low birth weight infants being weaned from IPPV. Seven studies were identified for inclusion

Treatments
Prophylactic methylxanthine (theophylline, aminophylline or caffeine) compared with control (placebo or no treatment).In four studies theophylline/aminophylline, in two studies caffeine and in one study both tested against each other)

Outcomes/endpoints
Successful extubation.

Statistical Methods
Results are expressed as relative risk (RR) and risk difference (RD) and from 1/RD the number needed to treat

Results
Recruitment/ Number analysed
Six trials, 172 infants.

Baseline data
There was a wide range of gestational ages and birth weights in the infants enrolled in the studies.

Efficacy results
Methylxanthine treatment resulted in a reduction in failure of extubation within one week (summary RR 0.48, 95%CI 0.32 to 0.71; summary RD -0.27, 95%CI -0.39 to -0.15; NNT 4, 95%CI 3 to 7; six trials, 172 infants).

Safety results
The number of infants with reported side effects was small and the differences not significant.

Conclusion
Authors' conclusions: Methylxanthines increase the chances of successful extubation of preterminfantswithin one week of age. Important neurodevelopmental outcomes are improved by methylxanthine therapy.
Caffeine, with its wider therapeutic margin, would be the better treatment to evaluate

against placebo.

Assessor's comments:
Caffeine preferable over theophylline to prevent apnoea in preterm infants after mechanical ventilation.

Henderson-Smart et al, 2010 (24)
Title: *Methylxanthine treatment for apnoea in preterm infants*

Description
Methods
Objective(s)
To determine the effects ofmethylxanthine treatment on the incidence of apnoea and the use of intermittent positive pressure ventilation (IPPV) and other clinically important outcomes in preterm infants with recurrent apnoea.

Study design
Cochrane review.

Study population /Sample size
Infants with recurrent apnoea. Six trials were identified.

Treatments
Three trials of theophylline and three trials of caffeine

Outcomes/endpoints
Primary outcome measures: Failed treatment (less than 50% reduction in apnoea, or use of IPPV, or death during study), use of IPPV and death before hospital discharge.

Statistical Methods
Results were meta-analysed using a fixed effect model and treatment effects were expressed as relative risk (RR) and risk difference (RD) and their 95% confidence intervals. For significant results, we used the inverse of the risk difference (1/RD) to calculate the number needed to treat (NNT).

Results
Recruitment/ Number analysed
Five trials of 192 infants.

Baseline data

Efficacy results
Methylxanthine therapy led to a reduction in apnoea and use of IPPV in the first two to seven days. These effect sizes are large although the sample sizes are low.

Safety results
In view of its lower acute toxicity (tachycardia or feed intolerance), caffeine would be the preferred drug.

Conclusion
Authors' conclusions: Methylxanthine is effective in reducing the number of apnoeic attacks and the use of mechanical ventilation in the two to seven days after starting treatment. Caffeine is also associated with better longer term outcomes. In view of its lower toxicity, caffeine would be the preferred drug for the treatment of apnoea.

Assessors comment:
There is some evidence that methylxanthines (caffeine and theophylline) are effective in the short-term for reducing apnoea in premature infants. Caffeine preferred due to lower toxicity.

MAH 5 conclusion:

1. The use of theophylline in the paediatric population is supported.
2. Dosage must be individualized, (target range: 8 - 20 mg/l) in order to achieve a dose that will provide maximum potential benefit with minimal risk of adverse effects.
3. The current CCDS (and therefore the SmPC) adequately describes the current knowledge and does not warrant any change.

4. Discussion

MAH 5 has provided four study reports with data concerning the efficacy and safety profile of theophylline in children.
The conclusion to be drawn from the reports are:

1. There is a marked inter- and intra-individual variation in regard to the pharmacokinetics of theophylline. This stress the need for individual dosing based on serum theophylline concentration levels measures. Therapeutic window 8 – 20 mg/L.
2. An unequal dosing might be well suited for children with 1/3 in the morning and 2/3 in the evening.
3. Theophylline has a limited clinical efficacy and a relatively high incidence rate of adverse events.
4. Recommended dosage in children (22 mg/kg) may cause serum theophylline levels to exceed the therapeutic level.

The studies provided confirm that the efficacy of theophylline is limited, and the indication for use therefore asthma *unresponsive* to standard treatment.

V. MAH 6 PIERRE FABRE

V.1 Information on the pharmaceutical formulation

MAH 6 has solely prolonged release products registered in Europe, THEOSTAT® 100mg, 200 mg and 300 mg in France and THEOPLUS® 100mg and 300mg in Czech Republic and Slovakia.
According to information in the submitted Bridging Report, theophylline is contraindicated in children less than 3 years.

Dosage will be adjusted for individual susceptibility on the basis of efficacy and adverse reactions. In children aged over 3 years, the average dose is between 10 and 16 mg/kilo in 2 intakes, morning and evening, given 12 hours apart.
MAH 6 states that measurement of plasma theophylline levels is not necessary in otherwise healthy children when doses less than 10 mg/kg/day are used. However, when higher doses are used or when drugs that may increase theophylline levels are also used chronically, plasma theophylline levels should be measured two hours before administration of the next dose once steady state has been reached (after 3 days). The recommended dose of theophylline in children over 3 years of age is stated to be 10 – 16 mg/kg.

V.2 Non-clinical aspects

No non-clinical studies were submitted by MAH 6.

V.3 Clinical aspects

1. Introduction

MAH 6 has submitted a clinical analysis of the use of theophylline in children, including two clinical studies in children sponsored by MAH 6: an efficacy study (Baculard et al) and a PK study (Paupe et al) and a brief literature review. MAH 6 has also submitted the most recent Summary Bridging Report, but not the current SmPC. The clinical analysis is largely based on the GINA (Global Initiative for Asthma) report, updated 2011(1).

2. Clinical studies

Baculard A et al, 1985 (2)
Title: ***[Management of childhood asthma with slow-release theophylline. Results of a multicenter trial in fourty-four patients treated for three months.]*** **Paper in French with English summary.**

Description
Open label efficacy study in children

Methods
Objective(s)
To study the efficacy of theophylline in children with severe asthma

Study design
Open label, uncontrolled trial.

Study population /Sample size
Fourty-four children with severe asthma.

Treatments
Prolonged released theophylline 16 mg/Kg/day twice daily. Dosage was rapidly increased to an average dosage of 20 mg/Kg/day and maintained during 3 months.

Outcomes/endpoints
Serum theophylline concentrations, clinical symptoms like rest dyspnea, dyspnea during exercise and wheezing scored 0-3.

Statistical Methods
Student's t-test

Results
Recruitment/ Number analyzed
Fourty-four patients.

Baseline data
Of the 44 patients, 28 were boys and 16 girls. Age range 4-16 years, mean (SD) 8.4 (3.7) years.

Efficacy results
Plasma concentrations stabilized from the second day of treatment with mean values between 9µg/ml before morning dose and 12 µg/ml 4 hours later.
Symptoms improved during treatment with theophylline. 47% of subjects became asymptomatic after 4 days of treatment and 61% after 3 months.

Safety results
Adverse events occurred in 15 patients. Adverse events were observed in 4 children assumed related to fever without adjustment in theophylline dosages. Theophylline withdrawal was decided for 3 patients because of adverse events.

Conclusion
Authors conclude that theophylline improves the lung function and has a low rate of adverse events.

Assessor's comments:
Efficacy study without a control group and clinical categorical data analyzed with student's t-test. Very limited scientific value. Adverse events in children with fever supports that fever may increase the serum concentration of theophylline and lead to overdosage.

Paupe J et al, 1985 (3)
Title: *[Serum theophylline concentrations after oral ingestion of Theostat 100 in children].* Paper in French with English summary.

Description
PK single dose study in children

Methods
Objective(s)
To investigate the pharmacokinetics of the slow release theophylline preparation Theostat 100 in children.

Study design
Pharmacokinetic study

Study population /Sample size
Five children

Treatments
Theophylline 8mg/kg 30 minutes after breakfast.

Outcomes/endpoints
Samplings were measured 0, 1, 2, 3, 4, 6, 12, 18, 24 and 36 hours later. Parameters studied were: elimination half-life, absorption constant, apparent elimination constant, area under curve 0-24h.

Statistical Methods
Descriptive statistics

Results
Recruitment/ Number analyzed
Five children.

Baseline data
Three boys and 2 girls. Age 5.5-12 years, mean (SD) 9.4 (2.7) years.

Efficacy results

TABLEAU III. — Paramètres pharmacocinétiques.

N° d'observation	Ka (h^{-1})	Kel (h^{-1})	T 1/2 (h)	AUC$^{24\,h}$ (mg/h^{-1})	AUC$_\infty$ (mg/h^{-1})
1		0,062	11,21	88,45	127,2
2	0,266	0,116	5,99	99,20	111,3
3		0,088	7,86	83,70	104,2
4		0,043	16,12	92,80	171,9
5	0,387	0,081	8,52	92,25	112,8
M ± SD		0,078 ± 0,028	9,94 ± 3,93	91,28 ± 5,573	125,5 ± 27,3

Safety results
No data

Conclusion
The study showed that administration of THEOSTAT tablets twice a day with 12 hours intervals, adjusting the dose in order to obtain a stable state and a concentration within the therapeutic range, was acceptable in regard to the pharmacokinetic parameters in children.

Assessor's comments:
Pharmacokinetic study of single dose in children. Ten blood samples from each child.

Barnes PJ et al, 1994 (4)
Title: *Theophylline in the management of asthma: time for reappraisal.*

Description
Review of the anti-inflammatory effects of theophylline in low doses that could give it a role in asthma management.

Methods
Objective(s)
To review the evidence that theophylline is more than a bronchodilator and discuss the future place of theophylline in the management of asthma.

Study design
Review

Results
There is increasing evidence that theophylline has several anti-inflammatory effects at concentrations which are therapeutically relevant (table 2).

Table 2. – Anti-inflammatory effects of theophylline

In vitro	
Mast cells	Decreased mediator release
Macrophages	Decreased release of reactive oxygen species
Monocytes	Decreased cytokine release
Eosinophils	Decreased basic protein release
	Increased/decreased release of reactive oxygen species
T-lymphocytes	Decreased proliferation
	Decreased cytokine release
Neutrophils	Decreased release of reactive oxygen species
In vivo	
Experimental animals	Decreased late response to allergen (guinea-pigs)
	Decreased airway responsiveness to allergen and PAF (guinea-pigs, sheep)
	Decreased airway inflammation after endotoxin and allergen (guinea-pigs, rats)
	Decreased plasma exudation (guinea-pigs)
Asthmatic patients	Inhibition of late response to allergen
	Increased $CD8^+$ cells in peripheral blood
	Decreased T-lymphocytes in airways

PAF: platelet-activating factor.

Conclusion
The author argues that it is sensible to reassess the role of theophylline and to design clinical studies to explore its potential as a disease-modifying agent. An important advantage of theophylline is its relative cheapness, and this is a significant consideration since asthma is a worldwide clinical problem.

Assessor's comments:
Further studies are required to evaluate the role of low-dose theophylline.
The role in the treatment of children is uncertain.

MAH 6 conclusion

The latest case reports presented in the Summary Bridging Report did not reveal any new safety data. MAH 6 concludes that the safety profile of THEOSTAT® in children is reflected in the section 4.8 and 4.9 of the current SmPC. However, MAH 6 states that due to several published case reports reviewed in the process of completing the analysis for the pdWS, the use of THEOSTAT® (which is known to have a tight safety margin) will be closely monitored in children and elderly patients in the Corporate Vigilances Division. On the basis of the clinical analysis and the safety analysis, no additional modification of the safety sections is foreseen mainly in children and consequently, MAH 6 does not have any proposals to modify the current SmPC for THEOSTAT® /THEOPLUS®.

3. Discussion

MAH 6 has submitted two clinical studies in children that were not included in the preliminary report. The studies do not add further to the knowledge of the use of theophylline in children.

VI. MEMBER STATES OVERALL CONCLUSION AND RECOMMENDATION

- **Overall conclusion**

The outcome of the assessment of this article 45 submission regarding theophylline including the MAHs answers to the questions raised is to recommend a harmonization process of the SmPCs with regard to paediatric dosing.

We recommend implementing a therapeutic interval of 5-12 µg/ml, with a note, that plasma concentration up to 20 µg/ml can be necessary to achieve efficacy in some cases. The product should not be administered to children below 6 months and the solid forms not to children below 6 years of age. The maintenance dose should be given in mg and plasma concentrations should be measured in case of insufficient effect of the recommended dose and in case of adverse events. Finally it should be implemented that fever may decrease the clearance of theophylline why it may be necessary to decrease the dose to avoid intoxication. Finally it should be added that theophylline is not first drug of choice in the treatment of asthma in children.

- **Recommendation**

Type IB variation to be requested from the MAH by October 8, 2013.

VII. LIST OF MEDICINAL PRODUCTS AND MARKETING AUTHORISATION HOLDERS INVOLVED

MAH 1 Mundipharma
Uniphyllin/Uniphyllin continus, prolonged-release tablets 200 mg, 300 mg, 400 mg and 600 mg
Theophyllin 200 mg Krugmann, prolonged-release tablets 200 mg and 400 mg
Theophyllin 600 mg, prolonged-release tablets 600 mg

MAH 2 Sanofi-Aventis
THEODEL 250 MG COMPRIME SECABLE, tablets 250 mg
THEOPHYLLINE BRUNEAU, prolonged-release tablets 200 mg
SOLOSIN, concentrate for solution for infusion 41.6 mg/ml
SOLOSIN RETARD, modified-release tablet 270 mg
SOLOSIN RETARD MITE, modified-release tablet 135 mg
SOLOSIN TROPFEN, oral drops, solution 104 mg/ml

MAH 3 Gebro
Theospirex retard, film coated tablets 150 mg and 300 mg

MAH 4 Biophausia
Theo-Dur, prolonged release tablets 200 mg and 300 mg

MAH 5 Nycomed
Euphyllin IV 200, solution for injection 20 mg
EUPHYLLIN 0,24 g, solution for injection 0.24 g
Euphylong, sustained release capsules 100 mg, 250 mg, 375 mg, 400 mg and 500 mg
Euphylong retard kapszula, sustained-release capsules 100 mg, 250 mg, 375 mg
Euphylong 200 i.v. injekció, solution for injection 200 mg
Euphyllin CR retard 250, coated tablets 250 mg
Euphyllin CR N, sustained-release capsules 200 mg, 300 mg and 400 mg
Eupyhyllin long, sustained-release capsules 200 mg, 300 mg
RESPICUR, solution for injection 200 mg
RESPICUR retard, capsules 100 mg, 200 mg, 300 mg and 400 mg
EUPHYLLINA RILCON, modified-released capsules hard 200 mg, 300 mg
EUPHYLLINA, prolonged-released tablet 250 mg
RESPICUR, prolonged-released capsule hard 200 mg, 250 mg, 300 mg, 375 mg, 400 mg

MAH 6 Pierre Fabre
Theostat, prolonged release tablets 100 mg, 200 mg and 300 mg
Theoplus, prolonged release tablets 100 mg and 300 mg