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Pharmacokinetic characteristics of a new liquid sustained-release formulation of theophylline designed for the elderly and children: Microcaps as sachet

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Abstract. A new sustained-release theophylline formulation was especially designed for the elderly and children. Microcapsules of theophylline, administered as a suspension in water, proved to be a suitable dosage form for a clientele with impaired or difficult deglutition. Pharmacokinetic characteristics of 2 batches at the lower (T_1) and upper (T_2) in vitro dissolution specification range of this new formulation and a pellet formulation (R) as a comparator were evaluated in an open, randomized, 3-way, multiple-dose, crossover study design with an asymmetric dosage regimen of 400 mg and 200 mg theophylline. Smooth and safe plasma concentrations with a high and long-lasting plateau were achieved with this new formulation. Plateau times which are independent of the asymmetric dosage regimen ranged from 16.4 hours (T_1) to 13.8 hours (T_2) and could therefore span sufficient time of the dosage interval. Maximum serum levels of 9.6 µg/ml and 10.0 µg/ml were attained 6.6 and 6.1 hours after dosing of T_1 and T_2, coinciding perfectly with the time of the critical morning dip at 2 – 4 a.m. With a nocturnal excess of 15.5% (T_1) and 17.9% (T_2) this circadian-tailored asymmetric dosage regimen proved to take into account the chronopathology of asthma and the chronopharmacokinetics of theophylline sustained-release preparations. Bioequivalence of all 3 formulations versus each other with regard to rate (C^{ss}_{max}) and extent (AUC^{ss}_{τ}) of absorption could be established for the 2 batches at the upper and lower in vitro specification range and for both batches of the new formulation compared to the reference. All in all, safety and efficacy of this new liquid prolonged-release theophylline could be established. Furthermore, in vitro specifications could be justified according to current EU guidelines.

Key words: theophylline – sustained-release liquid dosage forms – microcapsules – pharmacokinetics – asymmetric dosing

Introduction

Theophylline has a long and honorable history in the treatment of asthma [Frew and Holgate 1993], although its status has been reconsidered several times since its discovery in 1888. The development of β_2-adrenergic agonists during the 1960s, the introduction of inhaled preparations from 1969 onwards, and the emerging of inhaled steroids have resulted in a general shift away from theophylline in the hierarchy of asthma therapy. Nowadays, it has become increasingly clear that asthma is an inflammatory disease and that bronchoconstriction is a consequence of this process rather than being the primary element in asthma. This changed concept of the pathogenesis of asthma has triggered the reevaluation of theophylline therapy, combining bronchodilating, antiinflammatory, and immunomodulatory effects even at relatively low plasma concentrations [Barnes and Pauwels 1994].

In addition to the growing pharmacologic recognition, the principal limitation of the narrow therapeutic window has been overcome by the design of high quality sustained-release preparations. Two major ways to achieve a safe and controlled release of theophylline are by multiparticulate coated pellet technology and via monolithic matrices. Matrix technology commonly leads to a large geometry of these formulations causing great difficulties for the elderly and children with impaired or difficult deglutition. Pellets filled in capsules can be opened and sprinkled on soft food without a loss in bioequivalence. Nevertheless, opening a capsule and handling the single pellets is an unconventional and difficult technique, especially for the elderly.

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Additionally, the bitter taste of theophylline makes it unsuitable for children.

Therefore, the development of a fluid sustained-release preparation especially tailored for this clientele was initiated. Sustained-release microcaps incorporated in a sachet formulation can combine accurate dosing, easy handling, and a favorable taste. Even more importantly, this new formulation should meet the high pharmacokinetic standards set up for sustained-release theophylline formulations.

Methods

Ethics and regulatory aspects

This study was performed in the Clinical Research Centre of L.A.B., according to the principles and recommendations set forth in the revised Declaration of Helsinki, and WHO and FDA recommendations for the clinical evaluation of drugs. The study protocol was accepted without objections by the local ethics commission of Freiburg and by the ethics committee of the Bavarian chamber of physicians. Written informed consent was obtained from each volunteer after detailed verbal and written information on the aim and the possible risks of the study.

Subjects

Eighteen elderly, healthy volunteers of both sexes participated in this study. The age of the 8 male volunteers ranged from 57 to 74 years, the body weight from 59.0 to 69.4 kg. The age of the 10 female subjects ranged from 59 to 70 years, the body weight from 50.0 to 64.8 kg. Health was judged on the basis of medical history, physical examination, 12-lead ECG, and clinical laboratory screening. Additionally, all volunteers were screened for their metabolization status by a caffeine clearance test. Fast metabolizers with a caffeine clearance of > 2.5 ml/min/kg were excluded.

Study design

The objective of this study was to compare 2 sachet test formulations at the lower (T_1) and upper (T_2) in vitro specification range and a standard sustained-release preparation (R) with regard to rate and extent of absorption. For this purpose an open, randomized, 3-way, multiple-dose, crossover study design was selected. The study participants received, in an asymmetric regimen, 10 single administrations of 400 (2 × 200) mg and 200 mg of theophylline in the evening and in the morning, respectively. All treatments started with an evening dose of 400 mg at 8 p.m., followed by the consecutive morning dose of 200 mg at 8 a.m. After 5 cycles of evening and morning doses a 24-hour pharmacokinetic profile was obtained. The 2nd and 3rd phase followed immediately without a washout period. Blood samples were drawn immediately prior to the evening administration and 1, 2, 3, 4, 6, 8, 10, 12, 13, 14, 15, 16, 18, 20, 22, 24 hours after the last evening administration of each period. The sample size determination was based on an intrasubject CV of 12% (AUC) and 15% (C_{max}) as reported in literature on extended-release theophylline formulations [Steinijans et al. 1995]. Therefore, at a patient risk of 5% the chosen sample size of n = 18 was sufficient to limit the producer risk of incorrectly concluding inequivalence to 30% (power 70%) under the assumption of $0.9 < \mu T/\mu R < 1.1$ [Diletti et al. 1991].

Approximately 30 min before the drug administration dinner, respectively breakfast, was served. The standardized dinner preceeding the blood sampling period was identical for each period. The evening meal had a total energy of 4,276.6 kJ, with 36.2 g protein, 67.5 g fat, and 55.5 g carbohydrates. During and 24 hours before confinement only nonalcoholic and non-xanthine-containing beverages and meals were allowed.

Formulations

Both new formulations were designed as monodose sachets containing theophylline granules micro-encapsulated with ethylcellulose using a coacervation technology [Powell 1971]. A blend of saccarose, thickening agent, surfactant, flavor, and other excipients was added to the microcapsules. The thickening agent increases the viscosity of the suspension and avoids sedimentation of the microcapsules, thus enabling accurate dosing [Calanchi et al. 1986]. Prior to administration the sachet content was added to 100 ml of water and the resulting suspension was stirred up with a spoon. An extensively characterized formulation [Pabst et al. 1990, 1994, Wilson et al. 1991] with pellet technology was chosen as a reference formulation.

Analytical method

The plasma samples were analyzed for the concentrations of theophylline using a validated HPLC method. A calibration curve with 7 standard points was established and covered the range from 0.2 µg/ml to 20.0 µg/ml. The mean values for the accuracy as well as the precision of calibration standards and quality control samples measured during the whole study were not allowed to exceed ± 15% or maximal ± 20% at the lower limit calibrator and the lowest quality control sample. With an systematic error at the lower limit of quantitation of 2.01% with a coefficient of variation of 1.81% this analytical validation met internationally accepted standards [Shah et al. 1992].

Table 1 Definitions and calculations of pharmacokinetic parameters

Parameter	Definition	Calculation
extent characteristic		
AUC_{τ}^{ss}	area under the curve, over the complete dosing interval of 24 hours	linear trapezoidal rule
rate and shape characteristics		
C_{max}^{ss}	maximum concentration during the whole dosing interval of 24 hours	obtained from measured data
$C_{max,0-12}^{ss}$	maximum concentration during the first 12 hours of the 24-hour dosing interval	obtained from measured data
$C_{max,12-24}^{ss}$	maximum concentration during the last 12 hours of the 24-hour dosing interval	obtained from measured data
C_{av}^{ss}	average concentration at steady state	$C_{av}^{ss} = AUC_{\tau}^{ss} / \tau$, $\tau = 24$ h
$C_{av,2a.m-6a.m.}^{ss}$	weighted average concentration from 2 a.m. to 6 a.m.	$C_{av,2a.m.-6a.m.}^{ss} = \frac{C_{2a.m.} + 2 \times C_{4a.m.} + C_{6a.m.}}{4}$
C_{min}^{ss}	minimum concentration during the dosing interval of 24 hours	obtained from measured data
$t_{max,0-12}^{ss}$	time of maximum concentration during the first 12 hours of the 24-hour dosing interval	obtained from measured data
$t_{max,12-24}^{ss}$	time of maximum concentration during the last 12 hours of the 24-hour dosing interval	obtained from measured data
PTF	peak-trough fluctuation	$PTF = 100 \times (C_{max}^{ss} - C_{min}^{ss}) / C_{av}^{ss}$
$t_{75\%C_{max}}$	plateau time, time coverage of the concentration range from $0.75 \times C_{max}^{ss}$ to C_{max}^{ss}	obtained from measured data
nocturnal excess	excess of time-averaged nocturnal concentration over 24-hour average concentration	nocturnal excess $= 100 \times (C_{av,2a.m.-6a.m.}^{ss} - C_{av}^{ss}) / C_{av}^{ss}$

Pharmacokinetic evaluation

Pharmacokinetic parameters were calculated according to commonly accepted definitions [Schulz and Steinijans 1991, Steinijans et al. 1987] without assuming any specific model. Definitions and formulas of all parameters are presented in Table 1. In the following, arithmetic means are reported in the case of an additive model, i.e. for $t_{max,0-12}^{ss}$, $t_{max,12-24}^{ss}$, $t_{75\%C_{max}}$ and nocturnal excess; geometric means are reported in the case of the multiplicative model, i.e. for all other pharmacokinetic parameters. An estimate for the elimination rate constant, ke, was derived via log-linear regression from the concentration data of the terminal phase 18 hours up to 24 hours after the last dose.

Statistical evaluation

The decision to reject the null hypothesis of bioinequivalence, i.e. to conclude in favor of bioequivalence, was based on the inclusion of the shortest 90% confidence intervals for the ratio $\mu T_1/\mu R$ and $\mu T_1/\mu T_2$ of expected medians in the respective bioequivalence range. AUC_{τ}^{ss} was defined as the main target parameter with an acceptance range of 80/125% for bioequivalence. Furthermore, confidence intervals of treatment intervals were constructed and discussed for C_{max}^{ss} and $t_{75\%C_{max}}$. A multiplicative model was assumed for AUC_{τ}^{ss} and C_{max}^{ss}, whereas an additive model was selected for the evaluation of $t_{75\%C_{max}}$.

Results

Clinical observations

The study preparations were tolerated with no major problems. In 5 volunteers a hematoma at the puncture site of the indwelling catheter was observed. Eight volunteers reported adverse events other than a hematoma in one or more study periods. Above all, gastrointestinal symptoms, headache, and dizziness occurred which are well known adverse drug reactions during treatment with theophylline. With the exception of headache in 2 volunteers all adverse events reported were only of mild intensity.

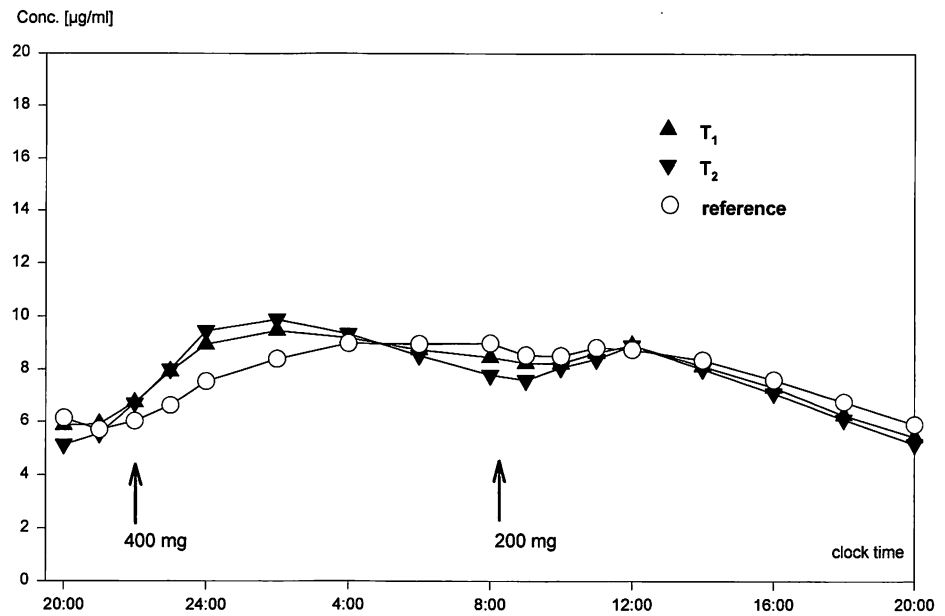

Fig. 1 Plasma levels of theophylline following asymmetric multiple dosing of 400 mg theophylline in the evening and 200 mg theophylline in the morning to 18 healthy male and female elderly volunteers.

Table 2 Pharmacokinetic characteristics (* = geometric/** = arithmetic mean) of theophylline following multiple oral administration of 400 mg and 200 mg b.i.d. in 18 healthy, elderly, male and female nonsmoking volunteers

Characteristic		Unit	T_2	T_1	Reference
AUC_τ^{ss}	*	(µg×h/ml)	183.4	186.2	183.2
C_{max}^{ss}	*	(µg/ml)	10.1	9.7	9.2
$C_{max,0-12}^{ss}$	*	(µg/ml)	10.0	9.6	9.1
$C_{max,12-24}^{ss}$	*	(µg/ml)	8.8	8.8	8.8
C_{av}^{ss}	*	(µg/ml)	7.6	7.8	7.6
C_{min}^{ss}	*	(µg/ml)	4.6	4.9	5.2
$t_{max,0-12}^{ss}$	**	(h)	6.1	6.6	9.7
$t_{max,12-24}^{ss}$	**	(h)	15.5	15.3	14.9
PTF	*	(%)	69.3	58.5	51.8
$t_{75\%C_{max}}$	**	(h)	13.8	16.4	17.3
nocturnal excess	**	(%)	17.9	15.5	12.6

Pharmacokinetics of a new sustained-release theophylline formulation

The mean plasma theophylline concentration/time profiles following twice daily administration, i.e. 400 mg at 8 p.m. and 200 mg at 8 a.m., are presented in Figure 1. Resulting pharmacokinetic parameters of all formulations under investigation are summarized in Table 2. Both sachet formulations generated comparable concentration time profiles. Maximum serum levels of 9.6 µg/ml and 10.0 µg/ml were reached 6.6 hours and 6.1 after the evening dose of 400 mg theophylline for T_1 and T_2, respectively. Maximum serum concentrations after the morning dose of 200 mg conformed with 8.8 µg/ml for both sachet formulations. For the whole dosage interval, mean average concentrations of 7.8 µg/ml and 7.6 µg/ml were calculated, ranging from minimum serum levels of 4.9 µg/ml and 4.6 µg/ml to maximum levels of 9.7 µg/ml and 10.1 µg/ml for T_1 and T_2, respectively.

As a consequence of the matching profiles, AUC_τ^{ss} for both sachet formulations were approximately analogous with 186.2 h×µg/ml (T_1) and 183.4 h×µg/ml (T_2). Plateau times, $t_{75\%C_{max}}$, were assessed in the mean as 16.4 hours for T_1 and as 13.8 hours for T_2.

The extent parameter, AUC_τ^{ss}, of the reference preparation was with 183.2 h×µg/ml in the same magnitude as both test formulations. For the reference formulation, maximum theophylline levels of 9.1 µg/ml and 8.8 µg/ml were attained 9.7 hours and 14.9 hours after the evening dose.

Discussion

Nowadays, high standards are set for new sustained-release preparations. Especially for theophylline as a model drug with a narrow therapeutic window the rate and extent of absorption should be carefully evaluated for new formulations. Although there is some controversy about the appropriate pharmacokinetic characteristics for this purpose [Hauschke and Steinjans 1993] AUC_τ^{ss} and plateau time $t_{75\%C_{max}}$ have been suggested as primary characteristics of extent and rate of absorption [Sauter et al. 1992, Schulz and Steinijans 1991]. Peak-trough fluctuation (PTF) is regarded as a further important rate characteristic

Table 3 Point estimates and 90% confidence intervals of pharmacokinetic characteristics for the ratios T_1/Reference; T_2/Reference and T_2/T_1 (* = following ln-transformation of the data).

T_1 versus reference parameter	Point estimate of the ratio T_1/Reference	90% confidence interval
C^{ss}_{max} *	104.6	98.3 – 111.3
AUC^{ss}_{τ} *	101.6	96.7 – 106.9
$t_{75\%C_{max}}$	94.9	86.5 – 103.2
T_2 versus reference parameter	Point estimate of the ratio T_2/Reference	90% confidence interval
C^{ss}_{max} *	109.1	102.5 – 116.1
AUC^{ss}_{τ} *	100.1	95.2 – 105.2
$t_{75\%C_{max}}$	79.5	71.1 – 87.9
T_2 versus T_1 parameter	Point estimate of the ratio T_2/T_1	90% confidence interval
C^{ss}_{max} *	104.3	98.0 – 111.0
AUC^{ss}_{τ} *	98.4	93.6 – 103.5
$t_{75\%C_{max}}$	83.8	75.0 – 92.6

for the evaluation of the product quality of a sustained-release theophylline preparation [Sauter et al. 1992]. Standard pharmacokinetic parameters, such as C^{ss}_{max} and C^{ss}_{min}, can be considered as valuable additional parameters to determine the safety and efficacy of a theophylline formulation.

For the generally accepted extent characteristic, AUC^{ss}_{τ}, point estimates of 101.6% and 100.1% for $\mu T_1/\mu R$ and $\mu T_2/\mu R$ were calculated with 90% confidence intervals ranging from 96.7 – 106.9% and from 95.2 – 105.2%, respectively. As this range is fully contained in the 80/125% region, bioequivalence with respect to the extent of absorption compared to the standard reference formulation can be concluded for both new sachet formulations (Table 3). For the parameter C^{ss}_{max}, customarily considered as characterizing the rate of bioavailability, bioequivalence compared to the standard formulation could also be proven. Again, confidence intervals of respective quotients were fully contained in the 80 – 125% range (Table 3), which is commonly used for the assessment of bioequivalence.

These results may be interpreted as indications of safety and efficacy of this new preparation, represented by 2 batches at the borders of the in vitro specification range. In addition, bioequivalence of the batch with the in vitro profile at the upper range of the specification (T_2) could be shown compared to the batch with the in vitro profile at the lower range of the specification (T_1). This "in vivo validation of in vitro specifications" is regarded as a further requirement for high quality theophylline preparations and ensures constant quality of the product.

Although equivalence could be shown for the rate (C^{ss}_{max}) and extent (AUC^{ss}_{τ}) of absorption, other relevant pharmacokinetic parameters allowed a discrimination between standard reference formulation and this new test formulations. Peak-trough fluctuations of 58.5% (T_1) and 69.3% (T_2) were increased compared to 51.8% of the reference formulation. For safe theophylline preparations a PTF < 50% is demanded by some authors for twice daily formulations following theophylline dosing in healthy male volunteers [Götz et al. 1994, Keller et al. 1994, Ukena et al. 1994]. Not all 3 formulations meet this requirement, but this shortcoming is not based on the formulations themselves but on the asymmetric dose regimen. Peak-trough fluctuations calculated for dose-adjusted twice a day 200 mg dose regimen resulted in PTFs of 30% (T_1), 39% (T_2) and 30% (R). Even considering an age-dependent clearance reduction in elderly volunteers, peak-trough fluctuations should not exceed the the critical safety margin of 50% and reflect the precise rate control of this dosage form.

Plateau times tendentially decreased from 17.3 (R) hours to 16.4 hours (T_1) and 13.8 hours (T_2), although the 90% confidence interval for T_1/R is fully contained in the 80/125% range and those for T_2/R and for T_2/T_1 in the 70/143% range (Table 3). Principally, plateau times should span as much as possible of a dosing interval in order to guarantee efficient theophylline levels for a long time. $t_{75\%C_{max}}$ of both new formulations was clearly increased compared to 11.7 hours reported in literature for asymmetric dosing [Reinhardt et al. 1987]. In addition, therapeutic levels can be maintained for a distinctly increased time span compared to 11.5 hours of a once daily regimen of theophylline [Götz et al. 1994].

This sufficiently long plateau time was not attained at the expense of nocturnal excess which is regarded as essential when treating asthmatic patients. Nevertheless, a complete loss of nocturnal excess must be anticipated for a balanced twice a day dosage regimen, whereas a nocturnal excess of approximately 35% can be achieved following once daily dosing of theophylline [Götz et al. 1994]. The asymmetric dosing of this study resulted in a nocturnal excess of 15.5% for T_1 and and 17.9% for T_2. Maximum theophylline serum concentrations were attained 6.6 hours (T_1) and 6.1 hours (T_2) after administration of the dose, coinciding perfectly with the morning dip in peak expiratory flow at 2 – 3 a.m.

Conclusion

Smooth plasma concentrations and a long-lasting plateau can be achieved with this new liquid sustained-release formulation, enabling a safe therapy of the antiinflammatory aspect of asthma within a narrow therapeutic window

of 5 – 20 µg/ml for 24 hours with a mean dosage of 10 mg/kg/day. Plateau characteristics such as plateau time and nocturnal excess, which are independent of the actual dosage given, were demonstrated to range between once a day and twice a day preparations on the market. Peak-trough fluctuations – even those for T_2 – are among the lowest for asymmetric twice daily dosing recorded in literature.

In addition, patients with nocturnal asthma can benefit from a circadian-tailored, unequal twice or once daily therapy aiming at higher serum concentrations at night when dyspnea is usually severe. The desired nocturnal excess can be achieved by doubling the evening dose as demonstrated in this study.

Therefore, this new galenical concept meets pharmacokinetic standards which are defined for sustained-release theophylline preparations. Combined with its easy mode of administration a suitable galenical alternative is now available not only for the elderly and children, but for all patients who have problems swallowing solid drug formulations.

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