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PHARMACOKINETIC EVALUATION OF A SUSTAINED RELEASE PREPARATION OF THEOPHYLLINE IN ASTHMATIC CHILDREN AND ADULTS

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A sustained release preparation of theophylline (SRP of Th) was evaluated pharmacokinetically in asthmatic children and adults and it was found to have good SR properties. Different dosage requirements for equal pharmacokinetic behaviour in these two groups have been explained by the influence of the factors which can be responsible, such as bioavailability, liver mass and free drug concentration.

INTRODUCTION

Chronic Th therapy is now well established as effective treatment of reversible airway disease in both children and adults. Significant improvement in

pulmonary function is usually achieved with serum Th concentrations between 7 and 20 mg/l, while at concentrations exceeding 20 - 30 mg/l serious toxic effects can occur. The need to maintain serum concentrations within the narrow range indicate that the use of pharmacokinetic principles in Th therapy is essential for proper patient management.In addition, Th pharmacokinetics is known to show large inter- and intra-subject variability (1). There have also been evidence of circadian variation of Th pharmacokinetics (2,3), influence of food (4,5) and age (6), but not gender (7).

Development and use of SRP of Th during recent years have made great improvement in Th therapy (8-10). SRP of Th, if completely and reliably absorbed, offer dual benefit of improved patient compliance due to longer dosing intervals, and reduction of the inter-dose fluctuations of serum concentrations. These formulations, especially recently developed beed-filled capsules, appear to be most useful in children. However, because of the complexity of SR formulations, their widespread use in all age groups has also caused recognition of host variables which may alter Th disposition. Since fluctuations in serum Th concentrations are a function of both the rate of absorption from the product and the rate of elimination of the drug from the patient, selection of the appropriate dosing regimen must include consideration of both the patient and the product (11).

The aim of this work was to evaluate a SRP of Th (micro-encapsulated beads in capsules) in both asthmatic children and adults, investigating pharmacokinetics of the preparation both after a single dose and at steady state.

SUBJECTS AND METHODS

Adult study

Nine hospitalized adult patients (5 female and 4 male) with reversible chronic obstructive pulmonary disease (COPD), mean age 53.2 ± 15.0 years (SD, range 27 - 64 years) and weighing 70.1 ± 4,2 kg (range 49.0 - 101.0 kg) participated in the study. Before the study, medical history, physical examination and routine laboratory tests were obtained from all the subjects. None of the patients had any evidence of cardiovascular, gastrointestinal, hepatic or renal disease. Each of them signed informed consent and the study was approved by the Clinical Ethical Committee. All the subjects abstained from alcohol and methylxanthine containing foods and beverages for at least 36 hours prior to and throughout the study. No other medication was given concomitantly with Th.

The subjects were on standard clinical protocol and were administered 2 equal doses of the SRP of Th at 12-hour intervals in a mean dose of 5.5 ± 1.0 mg/kg (SD, range 3.7 - 7.6 mg/kg).

Plasma samples (1 ml, heparin was used as an anticoagulant) were obtained at 0,0.5,1,2,4,6,8,10 and 12 hours after administration of the drug. The samples were frozen at -20°C until analyzed.

Pediatric study

Twenty six asthmatic children (9 temale and 17 male), mean age 10.0 ± 0.9 years (SD, range 3.5 - 15.0 years) and weighing 33.8 ± 3.0 kg (SD, range 22.0 - 72.0 kg) were included in the study. All the children were inpatients in the Hospital and from each subject informed parental consent was obtained. The study was approved by the Hospital Ethical Committee.

The children were on standard clinical protocol and were administered a mean Th dose of 8.0 ± 2.3 mg/kg (SD, range 5.0 - 11.0 mg/kg) as 2 equal doses at 12-hour intervals. All the subjects refrained from methylxanthine - containing food and beverages for at least 36 hours prior to and throughout the study. There was no any concomitant medication with Th.

Plasma samples (0.5 ml, heparin was used as an anticoagulant) were obtained just prior to dosing and 0.5,1,2,4,6,8,10 and 12 hours post dose. The samples were frozen at -20°C until assayed.

Methods of analysis

Th content in plasma was determined by the spectrodensitometric method (12).

The data were pharmacokinetically adequately analyzed by use of one - compartment model. Pharmacokinetic parameters considered after both a single dose of the preparation /$t_{1/2}$ - biological half - life, V_d - volume of distribution, Cl - total body clearance, C_{max} - maximum plasma concentration, t_{max} - time to reach C_{max} and MRT - mean residence time/ and at steady state /C_{max}, t_{max} and Fl(%) - percentage fluctuation during the dosing interval/ were calculated according to the literature for pharmacokinetic evaluation of SR preparations (13,14). Student's *t* - test was used for statistical comparison of the pediatric and adult data.

RESULTS

The mean concentrations of Th achieved in both group of children and adults after administration of a sustained release preparation in a single dose and at steady state, are given in Figure 1:

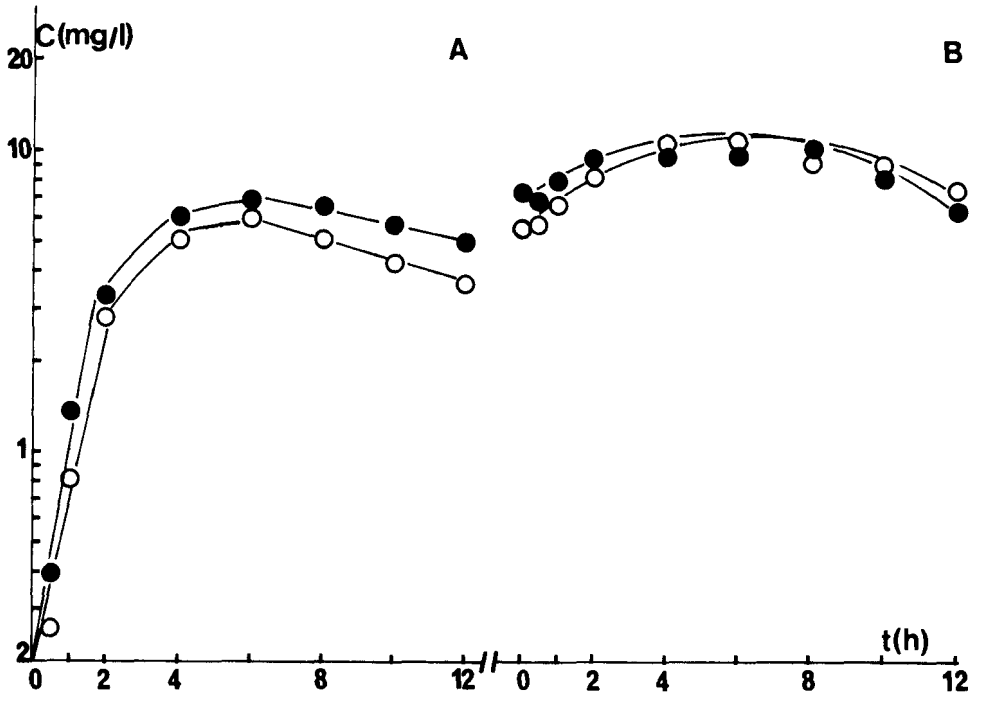

FIGURE 1

Mean concentrations of theophylline in 26 asthmatic children (●) and 9 adult patients (○) following administration of both single dose of a sustained release preparation (A) and at steady state (B).

Although the individual concentrations of Th after the equal dosage showed large variability, mean values in children are not significantly different from the mean values in adults ($p > 0.05$). However, mean dose given in the group of children was for about 45% higher than in the group of adult patients.

Corresponding pharmacokinetic parameters were calculated for both children and adults, and after both single dose and at steady state. Mean values of the

TABLE 1

Mean (±SD) pharmacokinetic parameters following administration of a sustained release preparation of theophylline to asthmatic children and adults - both single dose and steady state study.

	Pharmacokinetic parameter								
	Single dose						Steady state		
	$t_{1/2}$ (h)	Vd (ml/kg)	Cl (ml/h/kg)	C_{max} (mg/l)	t_{max} (h)	MRT (h)	C_{max} (mg/l)	t_{max} (h)	Fl (%)
CHILDREN	7.1	1058.1	130.4	7.8	6.9	12.9	11.2	5.6	72.0
	±2.7	150.7	76.0	3.7	1.8	0.3	3.3	1.0	9.0
ADULTS	8.1	1069.0	125.1	6.0	7.8	13.3	11.4	7.3	57.6
	±4.5	350.0	54.1	2.5	2.9	3.5	4.5	3.1	7.6

parameters calculated in each group of the patients are given in Table 1 (p.).

The values of all pharmacokinetic parameters calculated were not significantly different when compared between the groups ($p > 0.05$). Very similar maximum Th concentrations were achieved both in children and adults, and either after a single dose or at steady state. No significantly different time was necessary to achieve C_{max} in children and adults in either case. The amount of time required for intact drug molecule to move through the body - MRT was also not significantly different ($p > 0.05$). The percentage fluctuation (Fl) was in both children (72.0 $\pm$ 9.6, SD, range 24 - 138%) and adults (57.6 $\pm$ 7.6, SD, range 8 - 100%) lower than 100%, which is required for SRP of Th.

DISCUSSION

The mean values of Th concentrations in children and adult patients were not significantly different between the groups (Figure 1), but these concentrations were achieved with the dose of a SRP of Th in average for 45% higher in children than in adults. This does confirm that children require higher doses of Th on the mg/kg basis as some literature data indicate. Pharmacokinetic parameters calculated following administration of a SRP of Th (Table 1) show good SR properties of the preparation in both children and adults, as well as adequately chosen dosing interval (MRT, %Fl). However, none of the pharmacokinetic parameters calculated and compared between these two groups of the patients following administration of either single or multiple dose of the preparation was significantly different ($p > 0.05$).

One of possible reasons for the results obtained could be the difference in the number of patients in these two groups (9 compared to 26), as well as consistency of their age. In the group of asthmatic children only 5 patients were under age 5, while 21 of them were over age 5 where 12 of them were over 10. All the adult patients except just one were over 40 years, where 4 of them were over 60. However, when we tried to look at pharmacokinetics of Th dependent on age within the group of children, we did not find any significant difference. That could, at least partly, be due to a small and different number of subjects in each subgroup. Higher Th clearance in children found in some studies is proposed to be due to increased rate of metabolism of the drug, although neither metabolic pathway is differentially developed in children. It is supposed that the reason is greater liver mass-to-body mass ratio in children than in adults (15), which is certainly dependent on age and body mass and figure.

Further, there is only untested assumption that absorption, and consequently bioavailability, in children is similar to that in adults (16). It is now known that many factors from both SR products and patients can influence in vivo performance of these preparations, and for that reason they require special pharmacokinetic evaluation and consideration in the therapy, both in children and adults.

Third important fact which also could be responsible for the absence of signifficant difference in pharmacokinetics of the preparation between asthmatic children and adults, based on determination of total drug, is different availability of free (unbound) drug

in the body. Antal and col. (17) found that age - related changes in Th pharmacokinetics may not be evident when total (unbound plus bound) drug levels are measured, since change in protein binding with age may mask differences in V_d and Cl, and they emphasized the importance of including an assessment of plasma protein binding studies of drug disposition. This statement is supported by our findings on excretion of Th in saliva in children and adults (18), as it is considered that fraction of free drug in the total plasma concentration is proportional to the S/P (saliva/plasma) ratio (19). We found that about 80% of total Th determined in plasma is excreted in saliva in adults (P/S ratio about 1.3), while in children that percentage was for about 33% lower than in adults - it was about 60% (P/S ratio about 1.7). These results were consistent after intravenous and oral administration (single and multiple dose) of the drug, and indicate that there is constant presence of more free drug in the body of adults than of children, which may be one of reasons for lower doses requirements of adult patients compared to children.

As a conclusion, therapeutic use of sustained release preparations of Th in either children or adults does require constant monitoring, taking into account the factors which can alter their pharmacokinetics, such as bioavailability, liver mass and free drug concentration.

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