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PHARMACOKINETIC PROFILE OF TWO DIFFERENT PHARMACEUTICAL FORMS OF THEOPHYLLINE (A SLOW RELEASE TABLET AND A SYRUP) AFTER MULTIPLE DOSE ADMINISTRATION TO HEALTHY HUMAN VOLUNTEERS

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Due to the narrow therapeutic range of theophylline, plasma concentrations of this drug are monitored in patients undergoing chronic therapy. Slow-release preparations avoid the fluctuations in plasma levels and improve patient compliance. In this study, we have compared the pharmacokinetic profiles of a theophylline slow-release tablet and a syrup form, when administered in multiple doses to healthy adult volunteers. The classification based upon releasing patterns is confirmed.

Key words: theophylline – pharmacokinetics – plasma levels – slow-release preparation – humans

Theophylline (1-3 dimethyl xanthine) was introduced into therapeutics in 1900 and is a widely used drug in the treatment of asthma and acute bronchospasm (Hirsch, 1922). Aminophylline, an injectable form as ethylenediamine salt, was introduced ten years later (Herrmann et al., 1937). Apart from the bronchial musculature, other organs, tissues and systems have been described as targets for the action of theophylline (Atuk et al., 1967; Piafsky et al., 1977; Rall, 1982; Condino Neto et al., 1991). Supra-therapeutic concentrations in the central nervous system are responsible for important side effects, such as headache, convulsion and coma (Kordash et al., 1977). These later side effects together with the narrow therapeutic plasma concentration range have led to extensive studies of theophylline pharmacokinetics (for review see Hendeles & Weinberger, 1983). Since an important percentage of asthmatic patients are under chronic theophylline treatment, several slow-release preparations have been developed during the last ten years in order to increase patient compliance and to decrease plasma level fluctuations (Jonkman et al., 1984).

In this study we compare the pharmacokinetic profiles of two different commercially available theophylline preparations (a slow-release tablet and a syrup) administered to normal volunteers.

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MATERIALS AND METHODS

Subjects – Eleven healthy adult caucasian volunteers (6 males, 5 females), aged between 20 and 45 years (mean 26.5 ± 7.1), body weight 68 ± 13 kg (range: 50-92) and within 15% of their ideal body weight, were enrolled in the study. All subjects gave written informed consent, and the clinical protocol was approved by the University Hospital Ethics Committee. None of the selected volunteers was a smoker and all were free from significant cardiac, hepatic, renal, pulmonary, neurological, gastrointestinal, hematological and psychiatric diseases as determined by anamnesis, physical and psychiatric examination and laboratory screens. Female subjects were neither pregnant nor under contraceptional therapy.

Clinical protocol – The study was undertaken according to an open randomized two period crossover design with a two week washout period between each different preparation dose. For each treatment, volunteers were admitted at 7:00 pm and remained hospitalized for the following 48 hours. Each volunteer received four slow-release tablets (SR, Teolong-300 mg, lot No 955/900, Knoll, Brazil, one tablet every 12 hr) and five doses of theophylline syrup (SY, Teofilina Bermácia Solução, lot No 9057, Cia. Industrial Farma-

cêutica, Brazil, 30 ml equivalent to 200 mg, every 8 hr). Each tablet and syrup dose was taken with 200 ml of tap water. No solid or liquid food was ingested during the 2 hr before and after each dose administration. Xanthine or alcohol-containing drinks were prohibited during the protocol.

Sample analysis – Blood samples (3 ml) from an antecubital vein were collected into EDTA-containing tubes at 0, 0.25, 0.5, 1, 2, 4, 8 and 12 h after each SR dose, and at 0, 0.25, 0.5, 1, 2, 4, and 8 hr after each SY dose. Plasma concentrations were measured by reversed-phase ion-pair high-performance liquid chromatography (HPLC) with ultraviolet detection (wavelength: 273 nm), according to the method described by Weidner et al. (1980). Beta-OH-propyl-theophylline (Sigma Chemical Co., St. Louis, MO, USA) was used as internal standard. All samples from a single volunteer were assayed during the same day.

Statistical and pharmacokinetic analysis – The following pharmacokinetic parameters were analyzed: (i) – the maximum plasma concentration (C_{max}) reached after the first dose of theophylline (for SY this was first multiplied by the factor 1.5, which corrects for the ratio of the ingested doses, i.e. SR/SY = 300/200); (ii) – the time taken to achieve it (T_{max}); (iii) – ratio C_{max},/C_{min} (as an index of theophylline plasma levels fluctuation) after administration of the fourth SY dose or the third SR one, since at this stage each volunteer had already received 600 mg of theophylline of either formulation (C_{max}, is the maximum concentration achieved after the mentioned doses, and C_{min} is taken as theophylline concentration just before administration of this dose); (iv) – the time taken to reach a concentration equal to or higher than 10 μg/ml of theophylline (T_{10}), since this concentration is considered the threshold of the therapeutic concentration range (10-20 μg/ml).

C_{max} values (untransformed and logarithm-transformed) were analyzed by parametric (one-way ANOVA) or non-parametric statistical tests (Wilcoxon signed ranks) and the probabilities of the individual ratios being included within the range 0.8-1.2 were calculated by the two one-sided t-test. Individual T_{max}, T_{10} and C_{max},/C_{min} differences were also analyzed by the Wilcoxon non-parametric test. Other values are expressed as the arithmetic mean ± SD unless otherwide stated.

RESULTS

No side effects were reported by the volunteers during the clinical study. Physical examination and routine laboratory tests performed after the clinical study were unchanged compared with the pre-study results and were within the range of reference values. Those volunteers with an incomplete set of data (3 of 11, due to difficulties in blood sampling) were not considered for statistical analysis.

SR mean C_{max} was approximately 73% of the corrected SY value, as assessed by ANOVA of either ln-transformed or untransformed data (Table I). No significant differences were observed between periods ($p > 0.30$). The two-one-sided t-test showed that the probability of individual C_{max} ratios falling between 0.8 and 1.2 is around 20%, regardless of the mathematical treatment of these data. The lack of significant overlapping with the interval 0.8-1.2 was confirmed by non-parametric analysis of the individual C_{max} ratios (SR/SY). SR showed a significantly larger T_{max} when compared to SY (9.3 ± 2.7 hr vs. 1.8 ± 1.2 hr), and the 90% confidence interval of individual differences did not include zero when analyzed by non-parametric statistics (Table II).

TABLE I

Statistical analysis of C_{max} data

	SY C_{max} (μg/ml)	SR C_{max} (μg/ml)
Geometric mean	8.5	6.2
Arithmetic mean	8.7	6.4
S.D.	2.1	1.8
	SR/SY C_{max} ratio (r)	
Arithmetic mean	0.737	
Classical 90% CI	0.625 - 0.862	
Classical 95% CI	0.601 - 0.893	
$P\{0.8 < r < 1.2\}$	0.20	
$P\{r \leq 0.8\}$	0.80	
$P\{r \geq 1.2\}$	0.00007	
Geometric mean	0.733	
Classical 90% CI	0.632 - 0.851	
Classical 95% CI	0.610 - 0.882	
$P\{0.8 < r < 1.2\}$	0.16	
$P\{r \leq 0.8\}$	0.84	
$P\{r \geq 1.2\}$	0.0001	
Non-parametric 90% CI[a]	0.621 - 0.895	

a: according to Hauschke et al., 1990.
CI: confidence interval

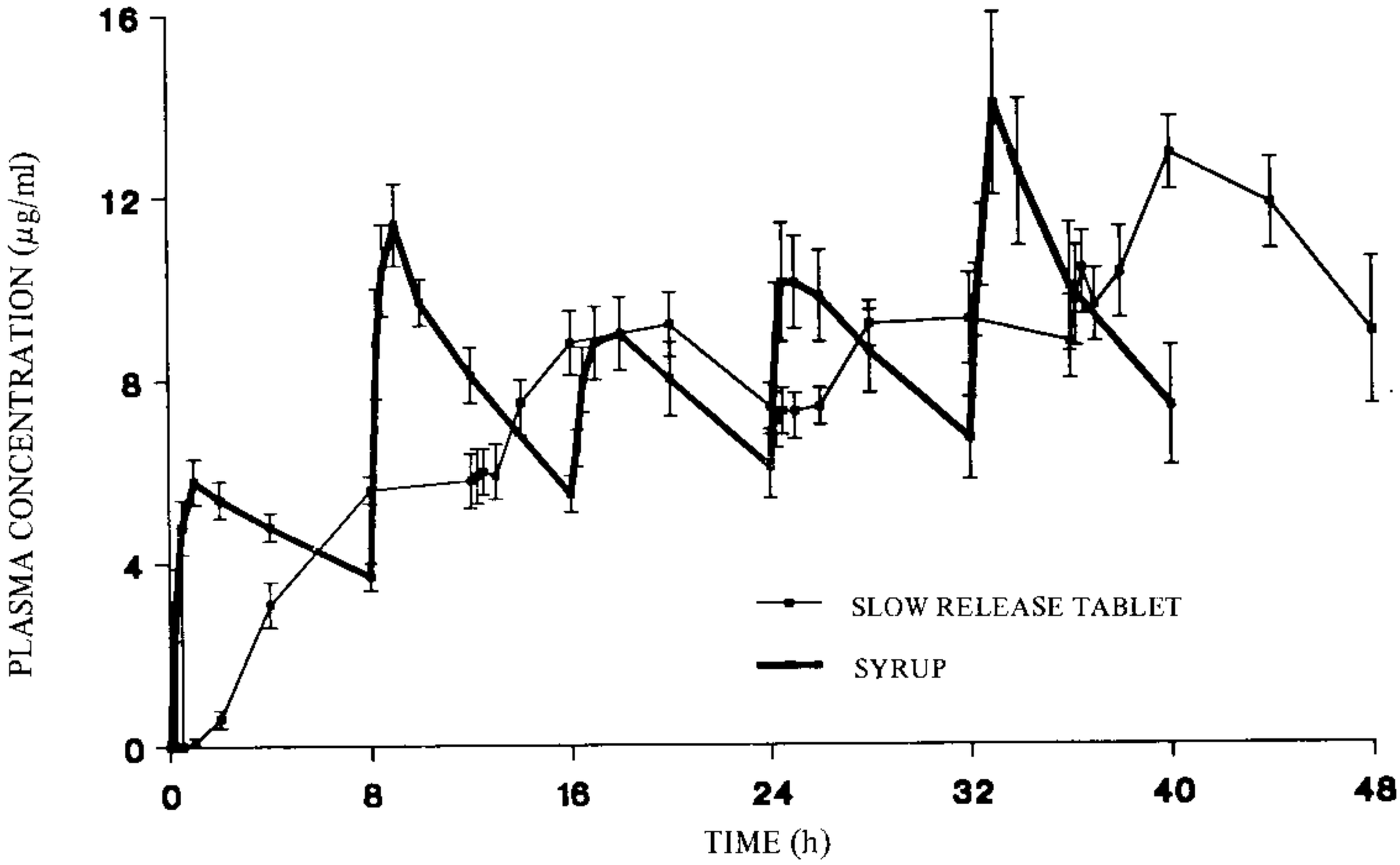
TABLE II

Statistical analysis of T_{max}, T_{10} and C_{max}'/C_{min} data

	SR T_{max} (h)	SY T_{max} (h)	SR T_{10} (h)	SY T_{10} (h)	SR C_{max}'/C_{min}	SY C_{max}'/C_{min}
Geometric mean	1.4	8.9	8.9	23.6	1.538	1.853
Arithmetic mean	1.8	9.3	9.0	25.9	1.578	1.889
S.D.	1.2	2.7	1.6	11.2	0.392	0.404
Median	2	8	8.25	28	–	–
Range	0.25 - 4	4 - 12	8.25 - 13	12 - 40	1.107 - 2.340	1.440 - 2.525

	(SR - SY) T_{max} differences	(SR - SY) T_{10} differences	(SR - SY) C_{max}'/C_{min} differences
Non-parametric 90% CI[a]	5.5 - 9.0	5.8 - 25.9	-0.712 - 0.177

a: according to Hauschke et al., 1990.
CI: confidence interval.



Plasma theophylline concentrations (mean ± SEM) vs. time curves obtained from 11 healthy adult volunteers after multiple dose administration of two different pharmaceutical forms of theophylline.

The same conclusions apply to T_{10} (SY: 9.0 ± 1.6 hr and SR: 25.9 ± 11.2 hr; Table II).

With respect to the ratios C_{max}'/C_{min} we were not able to demonstrate statistically significant differences (Table II). The pharmacokinetic profiles of both preparations are depicted in the Figure.

DISCUSSION

The degree of heterogeneity of the volunteer populations, as assessed by the variations observed in the pharmacokinetic parameters, was in accordance with that previously reported (Miller et al., 1984, 1985). Since tabagism is a principal cause of increased theophylline clearance, due to activation of the cytochrome

P450 mono-oxidase system (Jenne et al., 1972), special care was taken with respect to this variable when selecting the volunteers.

It has been reported that, in some cases, increments in theophylline dosage produce elevations in theophylline plasma levels higher than those predicted from the individual elimination rates due to decrease in theophylline clearance with increasing doses (Hendeles & Weinberger, 1983). Despite of the correction of C_{max} values by the ingested dose, SR mean C_{max} is lower than SY one. Taken together, the results on C_{max}, T_{max} and T_{10} confirm the classification of the preparations based on their releasing pattern, as also clearly illustrated by mean concentration vs. time curves (Figure).

T_{10} is not a conventional pharmacokinetic parameter, but we find it useful in terms of therapeutic applicability when comparing two pharmaceutical forms administered in multiple doses. Moreover, this parameter helps in deciding which of the forms would be more suitable for an acute bronchospasm.

Despite mean C_{max}/C_{min} ratios were not proved to be statistically different (Table II), our results shows the tendency towards slow release formulation being advantageous over the syrup, since plasma concentration fluctuations are reduced (as can also be seen in the Figure), thus minimizing the occurrence of concentration-related side effects.

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