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Comparative pharmacokinetic evaluation of sustained-release theophylline formulations in dogs and humans

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Summary

Several new sustained-release formulations of theophylline were developed and their sustained-release performance was evaluated in a comparative pharmacokinetic analysis. These new formulations, Theo-Dur, Theotrim and aminophylline were administered to 5 dogs and 6 healthy volunteers. Plasma levels of theophylline were determined by an HPLC assay. The absorption profiles of the various formulations were analyzed pharmacokinetically, using the Wagner–Nelson procedure. Two new formulations, Theotrim and Theo-Dur demonstrated very good sustained-release performance in humans and dogs. One formulation (T-2-A) showed incomplete absorption in both species, and its bioavailability relative to aminophylline was about 65% in humans and 78% in dogs. These results were also confirmed by the Wagner–Nelson Procedure. In this study the dog was found to be a good animal model as far as the rate and extent of absorption of the various tested theophylline formulations were concerned; the dog may be useful in primary screening of new formulations from this series.

Introduction

The search for improved therapy and patient compliance has led to the development of new formulations of old drugs or the formulation of new drugs which are administered less frequently than conventional dosage forms. Numerous studies have dealt with the development of animal models suitable for the investigation of the pharmacokinetics and the bioavailability of drugs and dosage forms (Ogata et al., 1982, 1984, 1985; Cressman and Sumner, 1971; Hecht et al., 1966).

Drug disposition and pharmacokinetic study in animals play an important role in drug discovery and development programs. It is now accepted that in vivo evaluation of chemical entities enhances our knowledge of oral absorption in humans. Safety data in animals or humans and their interrelation would be meaningless if the test drug did not reach the systemic circulation, or if there

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were no compartative pharmacokinetic data between species. The most widely used animal model is the dog which has been shown to demonstrate absorption similar to that in humans, even though the gastrointestinal transit time in dogs is shorter than in humans and the disposition of drugs might be different in the two species. The dog has been used successfully in various programs involved with the development of new formulations (Ogata et al., 1982, 1984, 1985, 1986; Aoyagi et al., 1982).

Oral theophylline therapy has been shown to be very effective in the treatment of lung diseases. In order to achieve maximum therapeutic benefit with a relatively low risk of severe side effects, the serum concentration should be maintained within the narrow range of 8–20 mg/l (Jenne et al., 1972; Mitenko and Ogilvie, 1973; Weinberger and Bronsky, 1974; Levy and Koysooko, 1975; Ogilvie, 1978). For a pharmaceutical formulation with a rapid absorption, the average short half-life of theophylline often requires a 6–8-h maintenance scheme to avoid large fluctuations in plasma concentration (Ogilvie 1978; Hendeles et al., 1978, 1985). With such a dosage regimen, lack of patient compliance is a serious problem, and low trough levels in the morning, with a possible risk of breakthrough of symptoms, can be expected. Therefore, sustained-release dosage forms of theophylline are very useful for maintenance therapy of chronic obstructive lung diseases (Hendeles et al., 1975). The bioavailability of certain sustained-release dosage forms of theophylline have shown to vary well below 100%, whereas other brands have been documented to be completely bioavailable (Mitenko and Ogilvie, 1973; Weinberger and Bronsky, 1974; Hendeles et al., 1985; Spangler et al., 1978).

This study was undertaken in order to evaluate the dog as an animal model for the pharmacokinetic analysis of sustained-release dosage forms of theophylline. Five sustained-release dosage forms of theophylline and a standard tablet of aminophylline were administered to 5 dogs and to 6 healthy volunteers. A comparative analysis was conducted between the pharmacokinetic parameters, and the sustained-release profiles of the various formulations were analysed in dogs and humans.

Materials and Methods

Three new experimental sustained-release formulations of theophylline, designated hereafter as formulations T-1, T-1-A, and T-2-A, were administered to 6 healthy subjects and 5 dogs. Formulations T-1, T-1-A and T-2-A were new sustained-release theophylline test formulations in a matrix tablet form. These formulations contained 300 mg of theophylline and a biodegradable polymer at a ratio of 1 : 0.25 (formulations T-1 and T-1-A) and 1 : 0.5 (formulation T-2-A). The granulates of formulations T-1-A and T-2-A were dried at 120 °C for 30 min. The granulates of formulation T-1 were dried at room temperature for 2 h. In addition, each subject and dog received a standard tablet of aminophylline and two commercial sustained release formulations of theophylline: Theotrim (Trima, Israel) and Theo-Dur (Key, U.S.A.).

The volunteers were male subjects, aged between 24 and 28 years and weighing 70–95 kg. They were selected for the study on the basis of negative medical history and physical examinations, normal routine blood chemical analysis and morphology, and urinalysis. Written informed consent was obtained from each volunteer. The entire clinical experiment was approved by the Helsinki Committee of the Hadassah Medical Center and the Israel Ministry of Health.

The animal studies were performed in 5 mongrel dogs, 3 males and two females, weighing 19–25 kg. In the dog study, each dog received in a randomized design, one tablet of 300 mg of each of the theophylline formulations and 200 mg of aminophylline. The same doses of theophylline were administered to the human subjects except in the case of aminophylline, where two tablets (2 × 200 mg) were given to each subject.

A washout period of 3 weeks was conducted between two consecutive studies in each subject (or dog). Each formulation was administered at 07.00 h following an overnight fast. Food was withheld for 5 h after the administration of the various theophylline formulations. In the human study, tea, coffee, coke and other caffeinated beverages and food were not permitted from the last two days before the beginning until the end of each study. Venous blood samples (4 ml) were

taken via an indwelling catheter from the forearm vein (in humans) or the cephalic vein (in dogs) at 0, 0.5, 1, 1.5, 2, 2.5 (in dogs), 3, 4, 5, 6, 8, 10, 12, 14, 16, 20 (in dogs), 24, 28 (in dogs), 30 (in humans), 32 (in dogs), 38 (in humans), and 48 h (in humans) after dosing. Plasma was immediately separated by centrifugation at 9000 rpm for 10 min and stored at −20 °C. Before assaying, the plasma was allowed to reach room temperature, vortexed, centrifuged and the residual clot removed. Plasma theophylline levels were determined by HPLC at an UV wavelength of 275 nm. The assay procedure was a modification of a previously reported method (Orcutt et al., 1977). Previous studies indicated the stability of theophylline in plasma at room temperature (Jonkman et al., 1981).

The linear terminal slope (β) of the log C (theophylline plasma concentrations) vs t (time) plot was calculated by the method of least squares. The half-life of theophylline ($t_{1/2}$ β) was calculated using the quotient $0.69/\beta$. The AUC (area under the C vs the t curve) was calculated using the trapezoidal rule, with extrapolation to infinity, by dividing the last experimental point by the linear terminal slope (Gibaldi and Perrier, 1982). The peak plasma concentration of theophylline (C_{max}) and the time to reach C_{max}, t_{max} were determined by inspection. The relative bioavailability (F) of theophylline was calculated from the ratio of AUC obtained after the administration of the various sustained release dosage forms of theophylline to that of aminophylline after normalization of the dose.

Results and Discussion

Mean plasma concentrations obtained after the single administration of the various theophylline formulations to humans and dogs are presented in Figs. 1 and 2. Tables 1 and 2 summarize the mean pharmacokinetic parameters obtained in the human and dog studies.

The absorption profiles of theophylline from the various formulations were calculated comparatively by using the Wagner–Nelson method (Wagner and Nelson, 1964). This method assumes

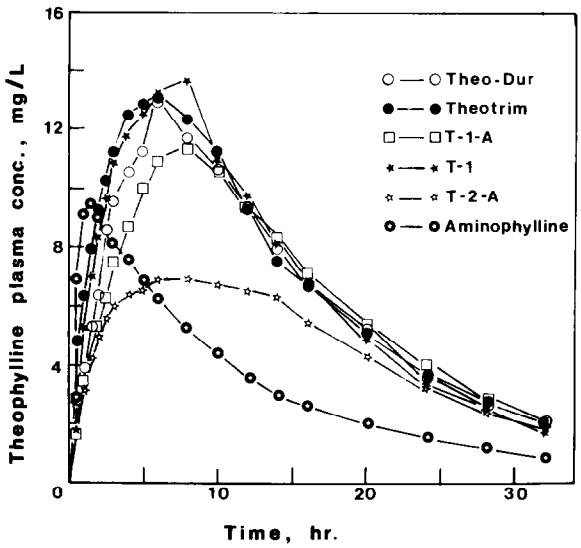

Fig. 1. Mean plasma concentrations of theophylline obtained after oral administration of 300 mg of Theo-Dur, Theotrim, and formulations T-1-A, T-1 and T-2-A and 200 mg of aminophylline to 5 dogs.

that the amount of drug absorbed at any given time point is equal to the sum of the drug amounts presented in the body and the amount eliminated by all routes. This method does not have any assumption regarding the kinetic order of the absorption, and thus it is very applicable for pharmacokinetic analysis of sustained release dosage forms. The mean percent absorbed–time plots of theophylline following each of the oral formulations are shown in Figs. 3 and 4. The absorption of theophylline after the administration of aminophylline was completed in 1.5 h in the dog and in 2 h in humans. After the administration of the sustained-release formulations of theophylline, the absorption was prolonged up to 12 h in dogs and humans. The experimental formulation T-2-A showed incomplete absorption in both species (70% in dogs and 55% in humans). These facts were confirmed by relative bioavailability calculated from the AUC data: 78 ± 31% in dogs and 65 ± 12% in humans. The sustained-release formulations: Theo-Dur, Theotrim, T-1 and T-1-A showed a similar rate and extent of absorption in dogs and humans. These four formulations showed a very good sustained-release profile.

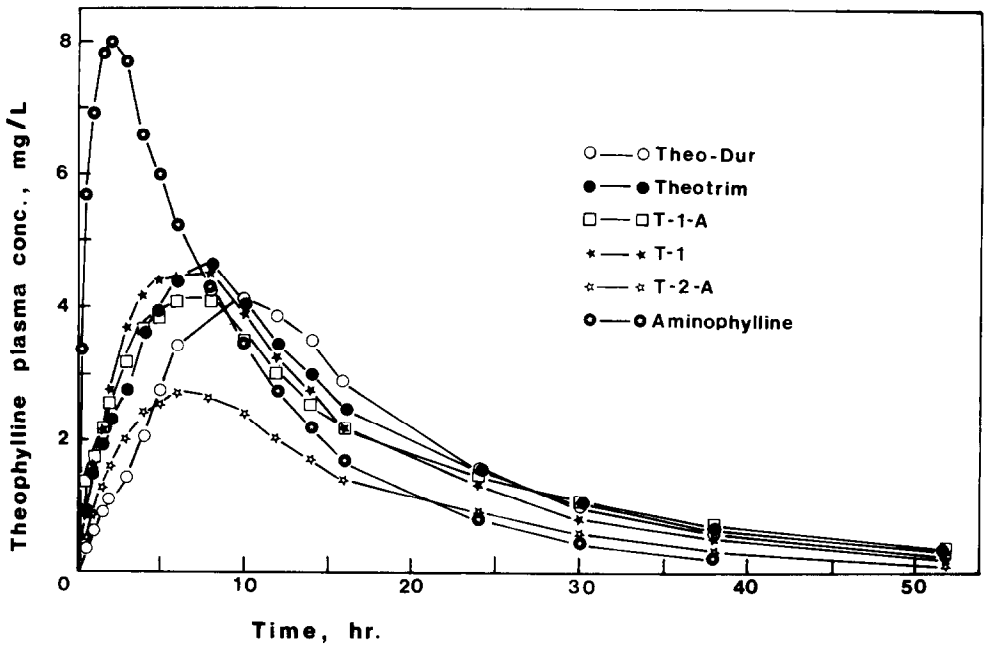

Fig. 2. Mean plasma concentrations of theophylline obtained after oral administration of 300 mg of Theo-Dur, Theotrim, and formulations T-1-A, T-1 and T-2-A and 200 mg of aminophylline to 6 healthy subjects.

TABLE 1

Summary of the mean pharmacokinetic parameters of theophylline obtained after administration of 300 mg of formulations: T-1, T-1-A, T-2-A, Theo-Dur, Theotrim and 200 mg of aminophylline (one tablet) to 5 dogs

Pharmacokinetic parameters	Aminophylline	Theo-Dur	Theotrim	T-1	T-1-A	T-2-A
β (h^{-1})	0.083 ± 0.014	0.082 ± 0.014	0.079 ± 0.011	0.088 ± 0.006	0.078 ± 0.019	0.072 ± 0.006
$t_{1/2}$ β (h)	8.6 ± 1.3	8.7 ± 1.6	9.0 ± 1.5	8.0 ± 0.5	9.4 ± 2.2	9.7 ± 0.9
AUC (mg · h · liter^{-1})	124 ±42	227 ±93	253 ±68	236 ±58	233 ±81	173 ±67
C_{max} (mg · liter^{-1})	9.6 ± 2.2	12.5 ± 4.6	13.0 ± 2.8	11.7 ± 2.6	13.0 ± 3.3	7.6 ± 1.6
t_{max} (h)	1.2 ± 0.5	7.0 ± 1.4	7.5 ± 1.9	8.0 ± 0.0	8.4 ± 1.7	8.4 ± 3.9
F (relative)	–	0.97 ± 0.14	0.97 ± 0.13	0.92 ± 0.09	1.02 ± 0.16	0.78 ± 0.31

Data are presented as mean ± S.D.

TABLE 2

Summary of the mean pharmacokinetic parameters of theophylline obtained after administration of 300 mg of formulations: T-1, T-1-A, T-2-A, Theo-Dur, Theotrim and 400 mg of aminophylline to 6 volunteers

Pharmacokinetic parameters	Aminophylline	Theo-Dur	Theotrim	T-1	T-1-A	T-2-A
β (h^{-1})	0.114 ± 0.030	0.080 ± 0.018	0.068 ± 0.022	0.072 ± 0.010	0.067 ± 0.017	0.078 ± 0.012
$t_{1/2}$ β (h)	6.7 ± 2.9	9.0 ± 2.3	11.0 ± 3.2	9.8 ± 1.7	11.0 ± 3.2	9.1 ± 1.5
AUC (mg · h · liter^{-1})	93 ±35	88 ±30	93 ±32	89 ±17	90 ±39	54 ±15
C_{max} (mg · liter^{-1})	9.2 ± 2.6	4.7 ± 1.5	4.7 ± 1.4	4.7 ± 0.6	4.2 ± 0.7	2.9 ± 0.5
t_{max} (h)	1.6 ± 1.0	9.0 ± 3.3	8.3 ± 1.5	7.9 ± 1.6	8.0 ± 1.3	7.2 ± 1.8
F relative	–	1.03 ± 0.17	1.10 ± 0.08	1.08 ± 1.60	1.05 ± 1.3	0.65 ± 0.12

Data are presented as mean ± S.D.

Previous experiments with sustained-release dosage forms of valproic acid (Bialer et al., 1984a, 1984b, 1985) and aminorex fumarate (Cressman and Sumner, 1971) showed that the dog is a good animal model for the absorption rate but not for the extent of absorption.

This study shows that in the case of theophylline the dog is a good animal model for predicting the extent and rate of absorption in humans. This can be attributed to the fact that the half-life of theophylline, unlike that of other drugs, is similar in dogs and humans, and the absorption of theophylline was not site-specific. Therefore, it could be prolonged for up to 12 h in both species. In addition, the similarity in extent and rate of absorption may be due to the fact that the absorption of theophylline was not affected by gastrointestinal pH.

This study shows that in the case of sustained release formulations of theophylline, results of studies in dogs can give reasonable information regarding the performance of these formulations in humans. Thus, unlike other drugs such as valproic acid or aminorex fumarate, in the case of theophylline sustained-release formulations, the dog can be used as an animal model in an a priori fashion and not only in an a posteriori one.

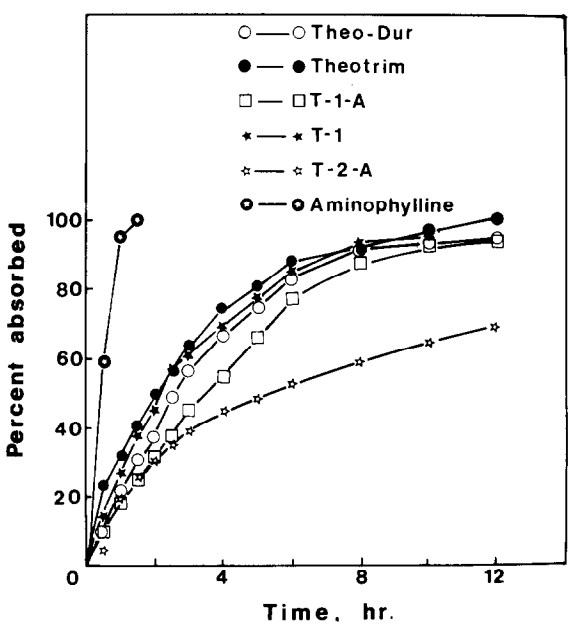

Fig. 3. Percent absorbed–time plot (mean data) of theophylline in dogs, after the administration of aminophylline, Theo-Dur, Theotrim and formulations T-1-A, T-1 and T-2-A.

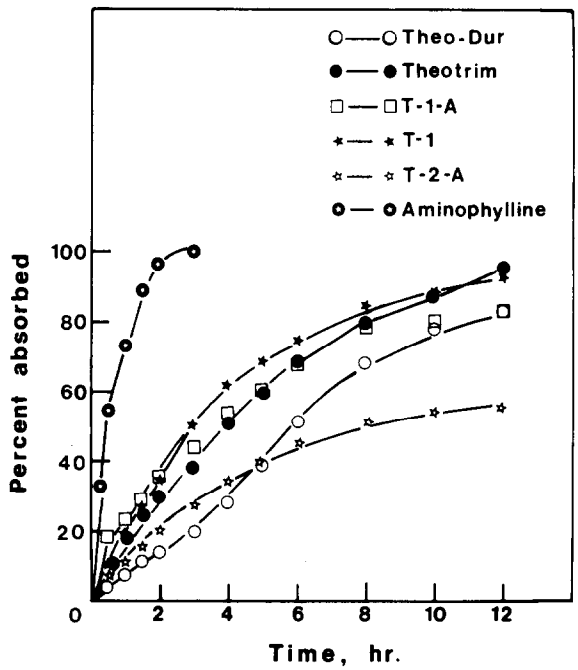

Fig. 4. Percent absorbed–time plot (mean data) of theophylline in humans, after the administration of aminophylline, Theo-Dur, Theotrim and formulations T-1-A, T-1 and T-2-A.

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