Theophylline Bioavailability in the Dog

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Abstract □ The bioavailability of theophylline following single oral doses of a theophylline capsule, a theophylline tablet, and an aminophylline tablet in beagle dogs was compared against an intravenous standard. Plasma theophylline levels after oral and intravenous drug administration were described by the one-compartment open model. The onset of theophylline absorption from the oral products was rapid. While the theophylline tablet showed a slower absorption rate than the capsule or the aminophylline tablet, all three products appeared to be completely bioavailable.

Keyphrases □ Theophylline—absorption, bioavailability in the dog, capsule, tablet, aminophylline tablet □ Bioavailability—theophylline absorption in the dog, capsule, tablet, aminophylline tablet □ Absorption—theophylline bioavailability in the dog, capsule, tablet, aminophylline tablet

The absorption of the bronchodilator theophylline from conventional and sustained-release dosage forms has been extensively studied in humans (1–11). In one study using an aqueous solution as a standard (5), the absolute bioavailability of 13 different types of theophylline tablets marketed in the United States was determined. All yielded an absorption of >90%.

Similar comparative bioavailability data in animal models are limited. The absolute bioavailability of theophylline from five commercial dosage forms in rabbits has been examined (12). In that study significant interproduct differences in the percent of dose absorbed were reported. The data showed no evidence of dose-dependent kinetics after single oral doses (65–200 mg) of capsules or tablets.

The present report concerns theophylline bioavailability in the dog following single oral doses of a theophylline capsule, a theophylline tablet, and an aminophylline tablet, using an intravenous aminophylline dose as a reference standard.

EXPERIMENTAL

A 1-year-old male beagle dog (dog 1, 11.4 kg) and a 2-year-old female beagle dog (dog 2, 11.7 kg) each received four single doses of aminophylline or theophylline in separate experiments. The dogs were fasted overnight predose and 4 hr postdose, but had access to water at all times. During the experiment, the dogs were initially placed in a restraining sling to facilitate accurate dosing and blood sample collection.

Intravenous Administration—Each dog received a single 50-mg aminophylline[1] (85% theophylline) dose by rapid injection into a cephalic vein. Blood samples (5 ml) were collected from a cephalic or femoral vein immediately before and at 7, 10, 15, 30, and 45 min and 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 hr after dosing.

Oral Administration—The capsule (A)[2] or tablet (B[3] or C[4]) was administered by placing it on the posterior portion of the dog's tongue so that it was not fractured or chewed before swallowing. The dose was followed by 20 ml of water. Venous blood samples were collected in the same manner as described for the intravenous dosing experiments, but the 7- and 10-min samples were omitted.

Blood samples were placed in heparinized tubes[5]. Plasma was separated by centrifugation and stored at −20° until analyzed.

Experiments were performed 3 weeks apart to avoid changes in pharmacokinetic parameters due to prior drug exposure and to allow complete drug washout from previous doses.

Plasma Assay—Plasma concentrations of theophylline were measured by reversed-phase high-performance liquid chromatography (HPLC) as previously described (13).

Data Interpretation—Plasma theophylline data after intravenous and oral dosing were analyzed in terms of the pharmacokinetic one-compartment open model. The equations and symbols pertaining to this model have been described (14). Intravenous pharmacokinetic parameters were calculated by linear regression of the natural log of the theophylline concentration against time. Oral data were analyzed on a digital computer[6] following standard graphical treatment; individual data sets were fitted to the appropriate equation by iterative least-squares methods using the NONLIN program (15).

RESULTS

Individual plasma levels of theophylline obtained from the four treatments are given in Table I. The results of the pharmacokinetic analysis are described in Table II.

Following intravenous dosing, plasma theophylline levels were highest (~5 μg/ml) at the first sampling time (7–10 min). Drug levels then declined monoexponentially, with plasma half-lives of 6.4 and 3.8 hr in dogs 1 and 2, respectively. The distribution volume, calculated from the y-intercept of the regression line, was 9.6 liter (84% of body weight) for dog 1 and 8.1 liter (70% of body weight) for dog 2. The plasma clearance was 1.5 ml/min/kg for dog 1 and 2.1 ml/min/kg for dog 2.

Following oral administration of each of the three products tested, theophylline was detected in plasma within 30 min. The observed onset was in good agreement with the computer estimated lag time of absorption (Table II). Product B appeared to be absorbed at a slower rate than products A and C, as indicated by its longer absorption half-time and time of peak concentration, although statistical comparison of data was not possible due to the small number of animals used. Normalized peak theophylline levels were similar for products A and B, but the level was lower for product C. The half-life of drug elimination was consistent between products, although variation between dogs was apparent. Plasma clearance values were calculated using the distribution volumes obtained from intravenous dosing.

Comparison of the areas under the plasma theophylline curves from the oral and intravenous doses, corrected for the different dose sizes, suggested complete absorption of theophylline from the three products. Correction for plasma clearance yielded F values of approximately unity in all cases.

DISCUSSION

Aminophylline, the ethylenediamine salt of theophylline, is generally used for the intravenous administration of this drug, primarily because of the low aqueous solubility of the weak acid (theophylline). A study using three volunteers (16) showed that, when given intravenously as aminophylline, theophylline was metabolized more rapidly and extensively than when given as the free acid. A previous study (17) compared the pharmacokinetics of theophylline and aminophylline after oral and intravenous administration in eight healthy male subjects, and reported virtually identical serum concentration–time curves for the two drug entities. While data in the present study also showed no apparent differences between aminophylline and theophylline disposition kinetics, plasma clearance was corrected for in the bioavailability calculations.

[1] Aminophyllin injection USP, 25 mg/ml, Gibco/Invenex, Chagrin Falls, Ohio.
[2] Elixophyllin (theophylline, 100-mg capsules), Berlex, Cedar Knolls, N.J.
[3] Theolair (theophylline, 125-mg tablets), Riker, Northridge, Calif.
[4] Aminophyllin (aminophylline, 200-mg tablets), Searle, Chicago, Ill.
[5] Vacutainer, Becton-Dickinson, Rutherford, N.J.
[6] IBM 370/168 digital computer, Rutgers Computer Center for Informational Services.

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Table I—Individual Plasma Levels of Theophylline

Hours	Plasma Theophylline, μg/ml							
	Intravenous		Oral					
			A		B		C	
	Dog 1	Dog 2	Dog 1	Dog 2	Dog 1	Dog 2	Dog 1	Dog 2
0.12	—[a]	5.0	—	—	—	—	—	—
0.17	4.6	—	—	—	—	—	—	—
0.25	4.6	4.8	0	0.4	2.7	0	2.3	1.0
0.5	4.3	4.5	0.3	4.5	5.3	0.2	16.0	9.3
0.75	4.1	—	4.7	9.2	7.5	0.5	15.6	13.0
1	4.1	4.4	10.9	11.4	8.9	1.7	16.3	15.1
1.5	4.0	4.2	11.3	11.0	13.4	6.6	12.9	14.9
2	3.7	3.9	9.3	9.7	13.8	13.9	13.0	17.2
3	2.8	3.1	8.9	8.0	12.6	12.6	13.0	14.5
4	3.0	2.5	8.7	7.6	12.3	10.4	10.4	11.9
5	—	—	8.1	—	—	—	—	—
6	2.3	1.8	7.5	5.8	9.8	8.6	10.5	9.5
8	1.7	1.2	5.4	4.0	7.6	6.7	7.1	7.5
12	1.0	0.6	4.0	1.8	4.6	4.1	3.5	3.7
24	0.4	—	1.6	0.6	2.0	0.6	1.1	0.6

[a] Not determined.

Table II—Pharmacokinetic Parameters Obtained from Plasma Theophylline Data

Parameter[a]	Intravenous		Oral					
			A		B		C	
	Dog 1	Dog 2	Dog 1[b]	Dog 2	Dog 1	Dog 2[b]	Dog 1[b]	Dog 2
D, mg	42.5	42.5	100	100	125	125	170	170
k_a, hr^{-1}	—[c]	—	2.8 (1.6–4.1)[d]	4.5 (2.8–6.3)	1.0 (0.61–1.4)	0.70 (0.16–1.2)	17.3 (−58.6–93.3)	2.2 (1.7–2.8)
$t_{1/2,abs}$, hr	—	—	0.24	0.15	0.69	0.99	0.04	0.31
k_{el}, hr^{-1}	0.11	0.18	0.092 (0.066–0.12)	0.16 (0.13–0.18)	0.12 (0.084–0.16)	0.16 (0.066–0.26)	0.12 (0.096–0.14)	0.14 (0.11–0.17)
$t_{1/2}$, hr	6.4	3.8	7.5	4.3	5.6	4.3	5.8	5.0
FD/V, μg/ml	4.4	5.2	11.5 (9.9–13.1)	12.4 (11.5–13.3)	18.0 (15.0–21.0)	17.8 (9.6–25.9)	16.6 (15.2–18.0)	19.7 (17.9–21.4)
t_0, hr	—	—	0.49 (0.48–0.51)	0.40 (0.35–0.45)	0.12 (0.0037–0.24)	0.73 (0.66–0.81)	0.24 (0.21–0.28)	0.22 (0.18–0.26)
r	0.99	1.00	0.98	1.00	0.99	0.96	0.99	1.00
Vd, liter/kg	0.84	0.70	—	—	—	—	—	—
F	1	1	1.1	1.0	1.4	1.2	0.93	0.94
Normalized AUC, (μg hr)/ml	40.4	29.0	53.1	33.0	49.6	37.7	34.5	35.1
PCl, ml/min/kg	1.5	2.1	1.3	1.9	1.7	1.9	1.7	1.6
C_{max}, μg/ml	—	—	10.3	11.0	13.4	11.5	16.0	16.3
t_{max}, hr	—	—	1.7	1.2	2.5	3.5	0.5	1.6

[a] D, dose of theophylline or equivalent; k_a, first-order rate constant for drug absorption; $t_{1/2,abs}$, half-time of absorption = $0.693/k_a$; k_{el}, first-order rate constant for drug elimination; $t_{1/2}$, half-life of elimination = $0.693/k_{el}$; F, fraction of dose absorbed; Vd, apparent distribution volume of theophylline in the body; t_0, lag time between dosing and the appearance of drug in plasma; r, correlation coefficient; Normalized AUC, area under theophylline plasma concentration *versus* time curve = FD/Vk_{el}, normalized to a dose of 42.5 mg theophylline; PCl, plasma clearance = Vk_{el}; C_{max}, maximum concentration of theophylline in plasma after oral dosing = $(FD/V)(k_a/k_{el})^{k_{el}/(k_{el}-k_a)}$; t_{max}, time at which C_{max} occurs = $\ln(k_a/k_{el})/(k_a - k_{el}) + t_0$. [b] Plasma concentration data were weighted by their reciprocals during computer analysis. [c] Not relevant. [d] The 95% confidence interval.

In experiments with rabbits (12), no dose-dependent theophylline pharmacokinetics after single oral doses in the 65–200-mg range were found. In the dogs used in the present study, elimination half-lives and distribution volumes following a 50-mg iv dose were similar to those obtained previously (18) after a 100-mg iv aminophylline dose. Therefore, the 50-mg iv aminophylline dose was adequate as a reference dose for oral bioavailability assessment. It should be noted, however, that dose-dependent characteristics in theophylline distribution and elimination were observed at higher doses (13.8–52.0 mg/kg of aminophylline) in guinea pigs (19) and in children (20, 21).

Although the decline in plasma theophylline levels after intravenous dosing is biphasic (22), the distribution of theophylline into peripheral tissues is so rapid that a one-compartment model has been shown appropriate for the analysis of data obtained in rabbits (12), dogs (18), and humans (23, 24). This was also the case in this study.

Based on the results shown in Table II, the GI absorption of theophylline is efficient in dogs given an oral dose of either theophylline or aminophylline, despite the lower aqueous solubility of the former. This observation supports previous findings in humans (2, 17). All three products studied here were immediate-release formulations. They were similar to each other with respect to the onset of drug absorption, but the absorption rate from the theophylline tablet (B) was slower than that from the theophylline capsule (A) or aminophylline tablet (C). However, all three products showed virtually complete bioavailability.

The efficient absorption of theophylline from these different dosage forms is consistent with available data in humans (5). However, experiments with rabbits showed erratic drug absorption from commercial tablets and capsules of theophylline or aminophylline; the same brand products as used in the present study yielded F values of 0.50 to 1.20 (12). Thus, the beagle dog appears to be a more appropriate animal model for conducting theophylline pharmacokinetic studies.

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COMMUNICATIONS

A New Technique for Determining *In Vitro* Release Rates of Drugs From Creams

Keyphrases □ Dosage forms, topical—new technique for determining *in vitro* release rates of drugs from creams □ Release rate, *in vitro*—new technique for determination, drugs from creams

To the Editor:

Within about the last 10 years, dissolution testing has become recognized as one of the most useful methods for evaluating tablets and capsules. In fact, such testing has all but supplanted the traditional disintegration test. Equipment and procedures for measuring the rate and extent of drug dissolution are now becoming standardized as a result of intensive research and, necessarily, some compromises.

No such standardization appears to be occurring, however, with the equipment or procedures used for testing the release of drugs from topical dosage forms (*i.e.*, creams, ointments, gels, suppositories, *etc.*). Many investigators have done extensive research on the release of drugs from such carriers, but it seems that, almost without exception, each used a unique method for presenting the drug to some receptor phase. The reason for this may be that each was faced with unique problems with regard to the formulations.

We present here a convenient and versatile technique for the *in vitro* testing of the release of drugs from creams or ointments. This technique could be used for a wide variety of vehicles, although it was developed specifically for cream formulations which are oil in water emulsions containing 0.01% estradiol.

The ideal procedure would be one in which the sample is in direct contact with the receptor phase, because barriers used to isolate the sample from that phase have a potential leveling effect on the rate of appearance of drug (in the receptor phase). Thus, the absence of barriers should maximize the probability of measuring differences between creams which differ only slightly in their drug-release characteristics. Therefore, we first tried filling shallow cups with the cream and immersing these in water at 37° in a fashion similar to that reported previously (1). This was attempted with a variety of cups of different dimensions supported upright or inverted in the receptor phase (water). These attempts failed because the cream swelled and eventually sloughed into the water. We noted also that the creams were no longer homogeneous, *i.e.*, the first few millimeters of sample nearest the water were physically different from the bulk of the sample before the end of the test time. In addition, samples were necessarily so large (a few grams) that only a small fraction of the total estradiol was near the surface where it could be expected to be released in a reasonable length of time.

Attempts were made to isolate the cream samples from the receptor phase using semipermeable membranes. Two membranes were tested, dialysis tubing and filter paper, in procedures similar to those reported previously (2). When these barriers were used, drug appeared in the receptor phase more slowly than when they were not. Although the problems associated with sample swelling and subsequent sloughing could be alleviated by using these barriers, this approach was abandoned because of the effects on the rate of appearance of drug in the receptor phase.

With these results in mind, we developed a simple technique which allows direct contact between the cream sample and the receptor phase (water) and which eliminates or minimizes sample sloughing. Cream samples are spread into the interstices of an 80-mesh stainless steel screen. The samples prepared in this way can be submerged in gently stirred water for long periods of time. The equipment and procedure are as follows.

A number of appropriately sized pieces of stainless steel screen were first prepared by cutting 7.5 × 7.5-cm squares and removing ~1 cm from each corner (Fig. 1).

Each screen was covered on both sides along the top edge with a piece of 2.54 cm wide masking tape such that 30 cm^2

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