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Absolute Bioavailability of Oral Theophylline

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The absolute bioavailability of theophylline was investigated by comparing the areas under concentration-time curves for intravenous theophylline with a plain uncoated anhydrous theophylline tablet and a theophylline solution.

Twenty asthmatic adults received approximately 7.5 mg/kg theophylline intravenously over 30 minutes; either seven days before or after the i.v. dose, 10 of these patients received tablets and the remainder solution in a similar dose. Blood samples were obtained at 0, 10, 20, 30, 45, 60, 90, 120, 180 and 240 minutes and then every two hours for at least 12 hours. Theophylline concentration was measured in serum by high-pressure cation exchange chromatography.

The fraction of the dose absorbed averaged 0.96 ± 0.03 for the tablet while the value for the solution was 0.99 ± 0.02. The time of peak absorption averaged 2 ± 0.3 hours for the tablets and 1.4 ± 0.3 hours for the solution. The maximum serum concentration attained was 15.3 ± 0.7 μg/ml after a dose of 7.6 ± 0.4 mg/kg of the tablet, and 14.6 ± 0.6 μg/ml after a dose of 7.3 ± 0.2 mg/kg of the solution. Absorption of the tested theophylline tablets and solution approached 100% of the available drug.

Key words: Bronchodilators; Dosage forms; Drugs, availability; Drugs, clinical effectiveness; Theophylline

Unreliable oral absorption of theophylline is a widespread misconception. Goodman and Gilman, for example, suggest that absorption of theophylline from the gastrointestinal tract is erratic because of poor aqueous solubility.[1] Although several studies have been published which compare blood levels of this compound administered in various dosage forms,[2–6] it is not possible to determine from these studies whether the differences in blood levels result from interpatient variation in disposition, the influence of the pharmaceutical formulation, or variability in the inherent absorption of this drug. None of these studies compared areas under the curve or other bioavailability parameters with a reference intravenous dose.

In contrast, Mitenko and Ogilvie, in an absolute bioavailability study of a sustained-release theophylline tablet, demonstrated that the mean amount absorbed in five normal male subjects was 77.1 ± 5.4% (range 59.2–91.6%).[7]

The present study was initiated to evaluate the bioavailability parameters of theophylline from hydroalcoholic and plain, uncoated tablet theophylline dosage forms. Thus, demonstration of complete bioavailability would suggest that any problem in absorption is formulation-related.

Methodology

Twenty asthmatic adult volunteers (10 men and 10 women) with a mean (±SEM)[a] age of 30 ± 2.1 years were studied. Theophylline was withheld at least 48 hours before each test day and absence of drug in the serum was confirmed by a blood sample obtained before administration of the test dose. The doses administered were calculated[b] to achieve serum theophylline concentrations of about 15 μg/ml assuming previously reported mean apparent volumes of distribution (500 ml/kg) and rapid distribution.[9,10]

All 20 patients received an intravenous dose of theophylline, 7.4 ± 0.22 mg/kg lean body weight, as Aminophylline, USP,[c] at a constant rate over 30 minutes using an IVAC-500 infusion pump. When delivery of the aminophylline was complete, the drug remaining in the i.v. tubing, approximately 11% of the total dose, was administered by a saline wash over a period of several minutes.

Seven days before or after the i.v. reference dose and following an overnight fast, the patients alternately received either a theophylline solution or tablet with 240 ml of water. The theophylline solution[d] was given to each of five men and five women in a dose of 7.3 ± 0.14 mg/kg. The tablets given to the remaining five men and five women were plain, uncoated theophylline tablets[e] in a dose of 7.6 ± 0.42 mg/kg. Food was not permitted until two hours after the oral dose.

Blood samples (5 ml) were withdrawn into Vacutainers containing no anticoagulant immediately before and at 10, 20, 30, 45, 60, 90, 120, 180 and 240 minutes and then every two hours for 12–14 hours after the start of the i.v. infusion or administration of the oral dose. Sera were separated and frozen until assayed. Serum theophylline was quantitated by high-pressure cation exchange chromatography.[11]

Areas under the serum concentration-time curves extrapolated to infinity ($AUC^{0\rightarrow\infty}$) were determined by the trapezoidal rule; the area from the last data point ($C\tau$) to infinity was estimated by the quotient of $C\tau$ and the beta disposition constant (β). Thus[12]

$$\int_0^{\infty} AUC = \int_0^{C\tau} AUC + (C\tau/\beta) \qquad (1)$$

The absolute bioavailability of the oral theophylline preparations was calculated as follows:[12]

$$[(AUC_{oral}^{0\rightarrow\infty})\ (D_{iv})\ (\beta_{oral})]/[(AUC_{iv}^{0\rightarrow\infty})\ (D_{oral})\ (\beta_{iv})] \qquad (2)$$

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[a] SEM = standard error of the mean.

[b] The dose was calculated by the following formula:[8] D = (apparent volume of distribution) (desired plasma concentration).

[c] Lot 345, Searle Laboratories, Chicago, IL 60680; USP assay = 20.6 mg/ml anhydrous theophylline.

[d] Theophyl-225 Elixir (5% alcohol), lot 0015, Knoll Pharmaceutical Company, Whippany, NJ 07981; USP assay = 7.5 mg/ml anhydrous theophylline.

[e] Theophyl-225 tablets, lot 13180015, Knoll Pharmaceutical Company; USP assay = 234.9 mg/tablet anhydrous theophylline.

where: D = dose (mg/kg); β = beta disposition constant (hr $-$ 1); and AUC = area under serum concentration-time curve ($\mu g \cdot ml^{-1} \cdot hr$).

Results

The fraction of the theophylline dose absorbed following administration of the 5% hydroalcoholic solution ranged from 0.88 to 1.12 with a mean of 0.99 ± 0.02 (Table 1). When given to fasting patients, the solution rapidly (1.4 ± 0.3 hours) produced a peak theophylline concentration which was within the therapeutic range for all patients (14.6 ± 0.6 μg/ml).

The fraction of the dose absorbed following administration of the plain, uncoated anhydrous theophylline tablets ranged from 0.75 to 1.05 with a mean of 0.96 ± 0.03 (Table 2); this was not significantly different from the oral solution. Peak serum theophylline concentrations following administration of the tablet averaged 15.3 ± 0.7 μg/ml at 2 ± 0.3 hours.

The areas under the concentration-time curves for both the solution and tablets were similar to those of the intravenous reference in both groups of patients (Figure 1). Absorption of the tablet appeared to be slightly slower which resulted in a lower mean peak concentration than that achieved with the intravenous dose in those 10 patients. For the elixir, absorption more closely paralleled the 30-minute intravenous infusion.

Discussion

Theophyllinization as a treatment for chronic asthma requires maintenance of therapeutic serum theophylline levels.[13] In order to avoid unacceptable fluctuations in serum theophylline levels, reproducibility of absorption characteristics is essential. Since incomplete absorption of drugs is likely to be associated with variable absorption even in the same individuals,[14] the absolute bioavailability is an essential characteristic to define for this drug.

The disarray of oral theophylline formulations includes liquid and coated bead-filled capsules, coated and uncoated

Table 1. Absorption Characteristics of a Theophylline Solution (10 Patients)

	Age (yrs)	Weight (kg)	Oral Dose (ml elixir)[a]	Oral Dose (mg)	Oral Dose (mg/kg)	I.V. Theophylline Dose[b] (mg)	I.V. Theophylline Dose[b] (mg/kg)	β (hr^{-1}) Oral	β (hr^{-1}) I.V.	AUC Oral	AUC I.V.	Oral Bioavailability Parameters f	T_p (hrs)	C_p ($\mu g/ml$)
Mean[c]	29	68	66	493	7.3	511	7.6	0.0871	0.0874	191.3	193.5	0.99	1.4	14.6
S.E.M.	2.2	3.8	3.9	29	0.14	161	0.17	0.009	0.008	20.4	18.8	0.02	0.3	0.6
Range	24–47	54–90	50–90	375–675	6.2–7.6	382–638	6.8–8.3	0.0428–0.1348	0.0579–0.1504	100.9–332.2	94.8–281.9	0.88–1.12	0.3–4.0	12.4–17.2

[a] USP Assay = 7.5 mg/ml anhydrous theophylline.
[b] Searle i.v. aminophylline; USP assay = 20.6 mg/ml anhydrous theophylline.
[c] Individual data on the 20 patients may be obtained by writing to the authors.
β = elimination rate constant.
AUC = area under concentration-time curve ($\mu g \cdot ml^{-1} \cdot hr$).
f = fraction of dose absorbed.
T_p = time to reach peak theophylline concentration.
C_p = peak theophylline concentration.

Table 2. Absorption Characteristics of Uncoated Theophylline Tablets (10 patients)

	Age (yrs)	Weight (kg)	Oral Dose No. Tablets[a]	Oral Dose (mg)	Oral Dose (mg/kg)	I.V. Theophylline Dose[b] (mg)	I.V. Theophylline Dose[b] (mg/kg)	β (hr^{-1}) Oral	β (hr^{-1}) I.V.	AUC Oral	AUC I.V.	Oral Bioavailability Parameters f	T_p (hrs)	C_p ($\mu g/ml$)
Mean[c]	32	73	2.25	528	7.6	464	7.3	0.1134	0.1036	173	183.6	0.96	2.0	15.3
S.E.M.	3.8	7.4	0.08	19.5	0.42	57	0.41	0.013	0.012	18.8	18.6	0.03	0.3	0.7
Range	22–57	51–134	2.0–2.5	470–587	4.4–9.2	383–616	4.0–8.3	0.0670–0.1989	0.0543–0.1889	88.1–283.4	95.4–286.6	0.75–1.05	0.75–4.0	12.9–20.0

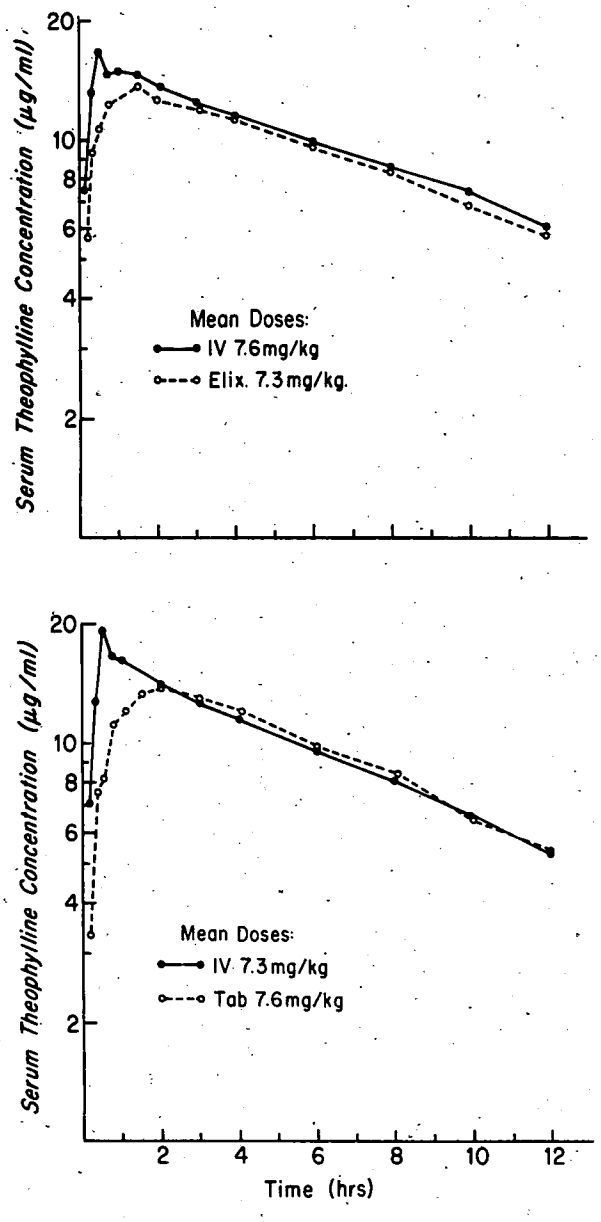
[a] USP Assay = 234.9 mg/tab anhydrous theophylline.
[b] Searle i.v. aminophylline; USP assay = 20.6 mg/ml anhydrous theophylline.
[c] Individual data on the 20 patients may be obtained by writing to the authors.
β = elimination rate constant.
AUC = area under concentration-time curve ($\mu g \cdot ml^{-1} \cdot hr$).
f = fraction of dose absorbed.
T_p = time to reach peak theophylline concentration.
C_p = peak theophylline concentration.

tablets, various other attempts at sustained release preparations, and hydroalcoholic and nonalcoholic solutions. Previous studies of plasma concentration-time curves suggest that these preparations can vary greatly in their rate, time of onset, and completeness of absorption.[2,3,6,7]

The present study demonstrates that the absolute bioavailability of theophylline from a low-alcohol solution and plain, uncoated tablets is nearly 100% with small interpatient variations in the rate and extent of absorption. This is in agreement with a paper recently presented by Coates et al[15] in which the absolute bioavailability of an aqueous solution of theophylline and a hydroalcoholic elixir was essentially complete. In contrast, the sustained release theophylline preparation studied by Mitenko and Ogilvie varied greatly in the rate and extent of absorption.[7] Such a preparation may exhibit unacceptable fluctuations in blood levels and would require investigation of this in more than the five patients examined in their study.

Erratic theophylline absorption thus would appear to be related to problems in pharmaceutical formulations, rather than variability in the inherent absorption of this drug. While definition of bioavailability characteristics is essential for appropriate selection of a solid dosage form, it is probable that the bioavailability of liquid dosage forms can be assumed to be complete. Plain, uncoated tablets with rapid and complete dissolution also may be generally reliable. Tablets or capsules with formulations that delay dissolution, however, require individual investigation to assure that the inherent bioavailability of theophylline has not been blocked by a poor formulaton.

Figure 1. Serum concentration-time profiles for a theophylline solution (top) and plain uncoated tablets (bottom) compared with intravenous theophylline in similar doses; the results are the means of 10 patients for each product



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