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In-vitro dissolution and in-vivo absorption of marketed sustained release theophylline preparations

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Summary

The dissolution behavior of two marketed sustained-release theophylline preparations was studied using the USP basket method. The pH of the medium was changed from simulated gastric fluid (pH 1.2) to simulated intestinal fluid (pH 7.5) after 1 h. A marked difference in the release pattern between the two brands was observed and was attributed to the difference in the nature and the method of manufacturing of both products. The bioavailability of these preparations was studied, using the salivary concentration, in six healthy male volunteers and the results were analyzed by the statistical moment theory. A significant difference in the absorption parameters was found, but there was no significant difference in the extent of absorption indicating that the two brands are bioequivalent. A direct correlation between the percent in-vivo absorbed and the percent in-vitro dissolved was observed for each brand.

Theophylline, a xanthine bronchodilator, has a narrow therapeutic index (10–20 mg/l) and is rapidly absorbed from the gastrointestinal tract. It has been formulated by various drug companies into sustained release products using different techniques in order to keep steady blood level within the therapeutic range for as long a period of time as possible. These products, even if they have the same quantity of theophylline, may not have the same pharmacokinetic profile due to different release mechanisms and dissolution rates. In order to evaluate these preparations, both in-vitro and in-vivo studies need to be carried out.

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The dissolution behavior of commercially available theophylline preparations was the subject of some recent studies (Buckton et al., 1988; Jalal et al., 1989). However, no bioavailability study was made to correlate the in-vitro dissolution with the in-vivo results. On the other hand, Weinberger et al. (1978), using the dissolution results of some theophylline preparations obtained from the manufacturers, could not find a close relation to either the rate or completeness of absorption of these formulations in adult volunteers.

In the present study the in-vitro dissolution and the in-vivo bioavailability of two commercially theophylline products are studied. The dissolution study was carried out using the USP XXI apparatus 1 at 100 rpm. The dissolution medium, at $37 \pm 0.5\,^{\circ}C$, consisted of 900 ml of simulated gastric fluid at pH 1.2 for 1 h, then substituted by

900 ml of simulated intestinal fluid at pH 7.5 for another 11 h. Both fluids were without enzymes. At predetermined time intervals 5 ml aliquots were withdrawn, and were immediately replaced with 5 ml of fresh dissolution medium equilibrated at 37°C. Theophylline concentration from the filtered samples was determined at 270 nm and the results were reported as the mean percent dissolved. Each point represents the average of six determinations. The in-vivo study was performed, under medical supervision, on six healthy non-smoking males capable of consent, aged between 30 and 50 years and weighing between 60 and 85 kg. All volunteers were instructed to abstain from xanthine or xanthine-containing food and drink as well as other medications for 24 h before and throughout the study. Subjects received, in a randomized, crossover design either Quibron^R (Mead Johnson, U.S.A.) or Theodur^R (Recordati, Italy) tablets (300 mg) after an overnight fast. A standard breakfast was served 3 h after dosing. Saliva samples (1–1.5 ml) were collected immediately prior to and periodically upto 36 hours after receiving the medication. The samples were stored at −20°C until analyzed by an HPLC assay. After equilibration to room temperature saliva samples were centrifuged at 5000 rpm (Gallenkamp CF-405, U.K.) for 10 min to separate any solid components. 400 μl of the supernatant were placed in centrifuge tubes and 100 μl aliquots of protein precipitant solution (2% $ZnSO_4$ in water) were added. The tubes were vortex mixed for 1 min and centrifuged at 15000 rpm for 15 min (Kubota KR-2000T). 30 μl of the supernatant were then injected into the chromatographic system (Waters Associates, Milford, MA) equipped with a WISP 710B sample processor, an M-730 data module, a 6000A pump and an M-481 variable-wavelength UV detector. A U-Bondapak C18 cartridge column (10 μm, 10 cm × 8 mm, i.d.) was used for the separation, using acetonitrile-phosphate (0.001 M K_2HPO_4) buffer (12:88 v/v) mobile phase adjusted to pH 4.2 at a flow rate of 3 ml/min. The effluent was monitored at 270 nm. Saliva theophylline concentration was determined with the use of calibration curve prepared on the day of sample assay. A 1 week wash-out period was allowed between the two products.

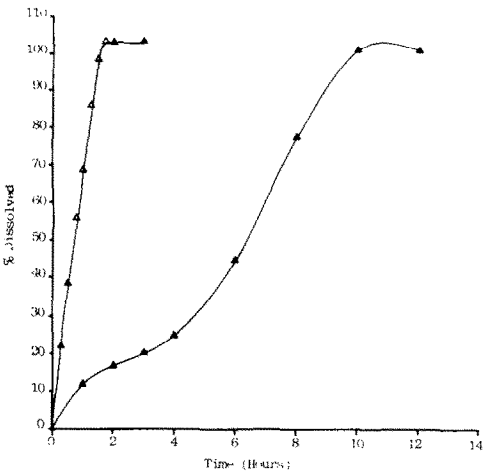

Fig. 1. Percent theophylline dissolved for Quibron (△) and Theodur (▲).

A distinct difference in the dissolution behavior between the two brands was observed (Fig. 1). This is indicated by the time for 50% theophylline release from both products (40 min for Quibron and 6.5 h for Theodur). Both products achieved 100% release during the time of study. However, while it took Quibron only 1.5 h for complete dissolution, Theodur required 10 h. A pH-dependent dissolution was observed in case of Theodur indicated by a change in slope at the 1 h point when the dissolution medium was changed from acidic to alkaline pH. This dependency was not seen in case of Quibron. The dissolution results in the simulated intestinal fluid were analyzed by three different equations, namely, zero-order, first-order, and the Higuchi model of drug release. It was found that Theodur was best fitted to a zero-order kinetics while Quibron was better represented by the Higuchi model.

The bioavailability data were analyzed using the statistical moment theory (Gibaldi, 1984). The use of mean saliva samples were found to give a good correlation with plasma theophylline concentrations (Jackson et al., 1983; Vaughan et al., 1988). In this study the pharmacokinetic parameters were calculated from the saliva theophylline concentration time curve. The maximum concentration, C_{max}, and the time to reach this maximum (t_{max}) were obtained directly from the individual salivary concentration curves. The area un-

TABLE 1

Pharmacokinetic parameters of theophylline after single oral administration of 300 mg slow release tablets

Product	Subject	C_{max} (μg/ml)	t_{max} (h)	AUC (μg h ml^{-1})	MRT (h)	MAT (h)	K_e (h^{-1})	K_a (h^{-1})
Theodur	GM	3.50	6.20	56.31	16.03	2.70	0.075	0.370
	AG	3.60	4.30	40.31	10.18	3.60	0.152	0.278
	MD	3.55	7.50	43.50	12.52	4.39	0.123	0.228
	SK	5.20	7.80	75.70	16.29	3.47	0.078	0.288
	AA	5.20	6.50	82.26	17.02	4.36	0.079	0.229
	KL	6.20	8.00	85.50	14.29	4.29	0.100	0.233
	Mean	4.54	6.72	63.98	14.40	3.80	0.101	0.271
	S.D.	1.146	1.380	18.840	2.630	0.675	0.031	0.055
Quibron	GM	4.65	5.60	66.56	13.20	2.51	0.094	0.398
	AG	3.40	4.50	44.10	10.57	2.17	0.119	0.461
	MD	3.80	4.50	54.03	11.99	3.06	0.112	0.327
	SK	3.92	4.00	71.46	16.60	2.52	0.071	0.397
	AA	5.00	4.20	104.60	21.04	2.17	0.053	0.461
	KL	3.10	6.00	51.96	17.14	1.44	0.066	0.503
	Mean	3.98	4.97	65.45	15.09	2.403	0.086	0.424
	S.D.	0.726	0.761	21.63	3.88	0.384	0.027	0.063
	t test	NS	S	NS	NS	S	NS	S

der curve from time zero to infinity (AUC) was calculated using the trapezoidal rule and the elimination rate constant calculated from the terminal phase of the curve. A paired t-test, at the 95% significance level, was used for the comparison of the individual pharmacokinetic parameters between Quibron and Theodur. The results are shown in Table 1.

A non-significant statistical difference in both the extent of absorption and the maximum saliva theophylline concentration was observed indicating that the two products are bioequivalent. However, a significant difference in time to maximum, t_{max}, and in theophylline concentration in the absorption phase (up to 3 h) was found. This difference can be attributed to the difference in the nature of the two products studied and the mechanism of drug release from each. This difference was further confirmed when the mean absorption time (MAT) for both preparations was compared and found to be significantly shorter for Quibron than for Theodur. A direct correlation between the percent theophylline absorbed (Gibaldi and Perrier, 1975) and the percent dissolved was found in the case of Theodur up to 4 h and in the case of Quibron up to 1.5 h when almost 100% theophylline was dissolved. However, the dissimilarity in the dissolution behavior of the two products did not reflect significant difference in the bioavailability of the two products.

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