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Short Communication

No effect of food on single dose bioavailability of sustained release theophylline (Sabidal); a comparison between Sabidal and choline theophyllinate solution

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The use of sustained release theophylline dosage forms is recommended because the drug has a rather short half-life of elimination and a rather small therapeutic range (about 7.5–20 $mg \cdot l^{-1}$).

As most asthmatic patients are in the worst condition during night time and early morning hours, theophylline plasma concentrations should be within the therapeutic range especially during these periods.

Though recent literature indicates that intake of a breakfast influences the absorption of theophylline from some sustained release preparations (Pedersen, 1981; Pedersen et al., 1982; Lagas et al., 1983; Thompson et al., 1983), it does not affect the absorption characteristics as observed with another brand (Leeds et al., 1982; Sips et al., 1984), and until now no information is available on the effect of the evening meal. Therefore, it was decided to study the influence of the evening meal on both rate and extent of theophylline absorption from sustained release theophylline tablets (Sabidal 270 mg). A comparison was made with choline theophyllinate solution containing 270 mg of theophylline.

The study had an open, cross-over design. It was a single dose experiment with a one week interval between administration of the medicaments.

On four occasions the following treatments were given at random.

(A) After a 6 h period of fasting a dose of 270 mg of theophylline was given as one tablet of Sabidal 270 mg (ZYMA S.A. Nyon, Switzerland), a sustained release

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dosage form containing 422 mg of choline theophyllinate. The sustained release properties of these tablets are based on slow diffusion through a micro-porous membrane.

(B) As under (A), but with concomitant intake of a standard supper.

(C) After a 6 h period of fasting, a dose of 270 mg of theophylline was given as a freshly prepared solution of 422 mg of choline theophyllinate in 150 ml of distilled water.

(D) As under (C), but with concomitant intake of a standard supper.

All dosage forms were taken at 19.00 h.

The supper consisted of soup (200 ml), a lean steak (125 g), gravy (of 12 g of margarine), boiled potatoes (200 g), fresh vegetables (200 g) and a dessert (150 g of vanilla custard) with a piece of cake (30 g), yielding a total energy of 3300 kJ, as 44 g (22%) of protein, 29 g (34%) of fat and 85 g (44%) of carbohydrates.

At 01.00 h on the next day a snack (2 pieces of cake and 150 ml of orange juice) was taken, at 08.00 h a standard breakfast, at 13.00 h standard lunch and at 18.30 h standard supper.

A complete absorption and elimination curve was evaluated by frequent blood sampling during a period of 27 h after drug intake.

Eight young, healthy, non-smoking human subjects (see Table 1), with normal cardiac, renal, hepatic, neurologic and gastrointestinal function, participated in this trial. No other drugs were taken for two weeks prior to and during the study.

Theophylline plasma concentrations were measured in duplicate by means of a selective HPLC method, a slightly modified version of the method developed by Jonkman et al. (1980). Other xanthines do not interfere in this assay.

Concomitant intake of food appears to have no significant effect on the absorption rate of theophylline from the Sabidal tablets. Plasma peak concentrations were reached after 4.36 ± 1.35 h (empty stomach, mean $\pm$ S.D.) and 3.87 ± 1.24 h (with food). (see Table 1 and Fig. 1.)

The unchanged absorption rate of theophylline from the sustained release tablets under both conditions can probably be explained by the fact that release of the drug from the tablets is slow to such an extent that the liberated drug will always stay in the dissolved state, even in the stomach. Apparently, the release of theophylline from the tablets is the number one rate-limiting step for absorption.

The amount of drug absorbed from the Sabidal tablets was hardly influenced by the presence of food; the mean AUC-value was slightly, but not significantly, decreased by the food (from 78.4 ± 21.0 mg $\cdot l^{-1} \cdot$ h to 68.4 ± 11.9 mg $\cdot l^{-1} \cdot$ h).

The absorption rate of theophylline from an aqueous solution, taken on an empty stomach, is about 4–5 times faster as compared to absorption from Sabidal tablets under the same conditions, mean values of t_{max} being 0.96 ± 0.59 h ($n = 7$) and 4.36 ± 1.35 h, respectively (see Table 1 and Fig. 1). Subject 3 showed unusually slow absorption when taking the solution under fasting conditions (with t_{max} 3.98 h), so in the mean value of t_{max} as represented here for the solution, the t_{max}-value of Subject 3 is deleted. Food, however, significantly decreased the absorption rate, t_{max} becoming 4.4 ± 0.75 h. Thus, on average, theophylline absorption in the presence of food was about 4 times slower.

TABLE 1

SUBJECT CHARACTERISTICS AND PHARMACOKINETIC PARAMETERS

Subject:		1	2	3	4	5	6	7	8	mean ± S.D.	*t*-test
Sex		F	M	F	M	M	M	M	M	–	
Age (years)		20	22	23	22	26	22	23	23	22.6 ± 1.6	
Weight (kg)		58	61	64	66	74	73	63	80	67.4 ± 7.5	
Dose ($mg \cdot kg^{-1}$)		4.66	4.43	4.22	3.91	3.65	3.70	3.91	3.38	3.98 ± 0.43	
c_{max} ($mg \cdot l^{-1}$)	A	8.22	6.69	6.72	5.26	4.16	4.92	6.17	4.90	5.88 ± 1.32	n.s.; $P > 0.05$
	B	7.13	7.61	7.12	4.72	4.52	5.58	6.47	2.56	5.71 ± 1.71	
	C	9.29	9.31	7.62	8.12	6.62	6.74	9.00	5.88	7.82 ± 1.32	s.s.; $P < 0.001$
	D	6.44	6.18	5.97	5.85	3.95	5.39	5.27	4.68	5.47 ± 0.83	
t_{max} (h)	A	4.90	2.50	5.92	5.92	2.50	4.02	4.05	5.08	4.36 ± 1.35	n.s.; $P > 0.05$
	B	4.02	2.97	2.98	5.97	4.02	2.00	3.98	4.98	3.87 ± 1.24	
	C	0.58	0.57	3.98	1.52	0.53	1.02	0.48	2.00	1.34 ± 1.20	s.s.; $P < 0.001$
	D	4.02	3.98	4.00	3.98	4.00	3.97	5.03	6.00	4.40 ± 0.75	
$(t_{1/2})_{el}$ (h)	A	6.4	6.1	5.6	8.8	5.9	6.1	6.5	8.5	6.7 ± 1.2	n.s.; $P > 0.05$
	B	5.6	6.4	5.9	7.7	5.2	6.3	6.9	8.9	6.6 ± .12	
	C	5.3	6.0	6.0	7.3	4.4	5.6	7.6	8.5	6.3 ± 1.4	n.s.; $P > 0.05$
	D	6.9	6.9	5.8	8.9	4.7	6.0	6.5	7.6	6.7 ± 1.3	
$AUC_{0 \to \infty}$ ($mg \cdot l^{-1} \cdot h$)	A	112.7	73.1	77.4	97.3	44.2	60.1	82.3	79.8	78.4 ± 21.0	n.s.; $P > 0.05$
	B	81.5	77.5	72.6	73.3	45.8	60.9	75.7	60.2	68.4 ± 11.9	
	C	86.3	83.1	87.3	94.3	45.2	64.8	92.1	87.8	80.1 ± 16.7	n.s.; $P > 0.05$
	D	86.7	83.8	71.0	97.6	40.7	65.5	72.9	70.1	73.5 ± 17.0	
$F_{D/C}$		100.5	100.8	81.3	103.5	90.0	101.1	79.2	79.8	92.0 ± 10.7	
$F_{B/A}$		72.3	106.0	93.8	75.3	103.6	101.3	92.0	75.4	90.0 ± 13.8	
$F_{A/C}$		130.6	88.0	88.7	103.2	97.8	92.7	89.4	90.9	97.7 ± 14.3	
$F_{B/D}$		94.0	92.5	102.3	75.1	112.5	93.0	103.8	85.9	94.9 ± 11.5	
$F_{B/C}$		94.4	93.3	83.2	77.7	101.3	94.0	82.2	68.6	86.8 ± 10.8	

A = Sabidal tablet without food; B = Sabidal tablet with food; C = solution without food; D = solution with food.

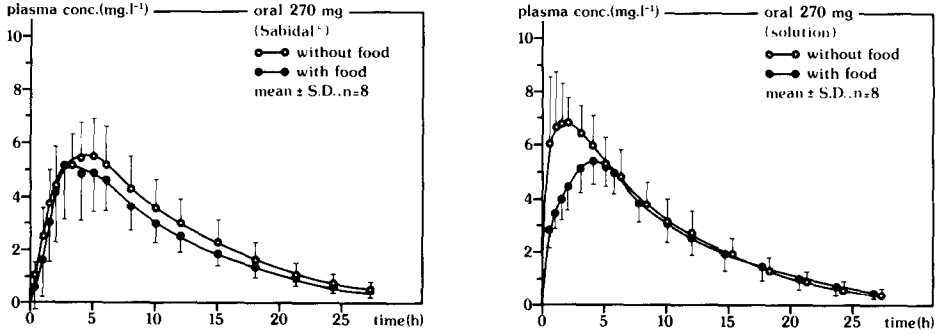

Fig. 1. Mean theophylline plasma concentration–time curves as obtained after intake of the Sabidal tablet and the choline theophyllinate solution with and without concomitant intake of food.

Partially, delayed absorption in the presence of food may be caused by the lower solubility of theophylline (weak acid) in the stomach, where the drug will stay together with food for a few hours. Furthermore, the food mass may create a physical barrier between the drug and the gastrointestinal epithelium as was earlier suggested by Welling et al. (1975) in their study on the influence of diet and fluid on bioavailability of theophylline.

The amount of drug absorbed, when given as a solution, was affected by concomitant food intake to a similar extent as was observed after administration of Sabidal tablets: the AUC decreased from 80.1 ± 16.7 mg $\cdot l^{-1} \cdot$ h to 73.5 ± 17.0 mg $\cdot l^{-1} \cdot$ h.

Apparently, the bioavailability of both dosage forms is decreased with about 10% by concomitant intake of food.

The relative bioavailability of the Sabidal 270 mg tablet, as compared with the solution, is essentially complete under fasting conditions ($F_{A/C} = 97.7 \pm 14.3\%$). Intake of food did not considerably reduce relative bioavailability ($F_{B/C} = 86.8 \pm 10.8\%$) of the tablets; as compared with the solution, taken with food, it accounted for $94.9 \pm 11.5\%$ ($F_{B/D}$).

For both dosage forms no influence of food was seen on the elimination rate of theophylline, as is shown by the mean values for half-life of elimination.

From our results, it can be concluded that the presence of food slightly reduces the extent of absorption of the drug as such. While the rate of absorption from an aqueous choline theophyllinate solution is delayed about four times, the release properties and subsequent absorption characteristics of the sustained release dosage form Sabidal were hardly affected by the presence of food.

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