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Note

Influence of sorbitol solution on the bioavailability of theophylline

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Summary

Solutions of sorbitol can modify the absorption of theophylline. Data show that after oral administration of theophylline dosage form with water and sorbitol solution the C_{max} and $AUC_{0-\infty}$ values were similar, indicating that the drug is essentially completely absorbed. However, the t_{max} values were significantly different ($p < 0.05$). A maximum absorption rate with peak levels prior to 1.30 h was obtained when theophylline was taken with water following fasting. Dosing with sorbitol solution, however, increased the time for attainment of the maximum plasma concentration to 2.10 h. The delayed attainment of t_{max} may be due to both reduced gastric emptying rate or retardation of the flux of drug across the gastric mucosa. It is speculated that the shrinking of the lateral intercellular spaces of the duodenal enterocytes mediates and controls the slowing of gastric emptying and flux from lumen to intercellular space.

The rate of drug absorption and the onset of pharmacological response for the majority of drugs are often directly related to the rate at which drugs pass from the stomach to the intestine. Therefore, any factor which influences the rate of gastric emptying, intraluminal transit or mucosal uptake, may influence the rate of absorption, plasma concentration and onset of action of an orally administered drug. Many of the factors regulating drug absorption are known and a variety of the physiological, pathological and pharmacological factors influencing gastric emptying rate have been investigated (Nimmo, 1976). There are reports indicating that the calorie content, pH and calcium sequestering capacity as well as volume and possibly the osmotic pressure of solutions are important determinants of the rate of absorption, partly because of their influence on gastric emptying (Kato et al., 1969; Houston and Levy, 1975). Although reliable drug dosage forms are now available, significant inter-individual variability in the pharmacokinetics of many drugs is common, which may result in either subtherapeutic or toxic levels of drug in some individuals and/or delayed attainment of t_{max} due to slow absorption in others. Kato et al. (1969) found that the absorption of aminopyrine and dipyrone was slower when administered with sucrose and D-sorbitol and concluded that the high osmotic pressure of the

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sucrose solutions caused a delay in gastric emptying. On the other hand, the passive transfer of riboflavin, salicylate and sulphanilamide across everted rat intestine was found to be inhibited by the presence of glucose in solution (Mayersohn and Gibaldi, 1971).

The effect of certain sugars on drug transport directly correlated with an effect on fluid uptake by the intestinal membranes and tissues. Glucose and xylose, at a concentration of 250 mM, both caused an increase of 149 mg water/g of tissue from a tissue fluid uptake of 52 mg/g of tissue in the control solution. The increase in compartmental cellular volume of the intestinal tissue in the presence of the inhibitors may result in a decrease in effective drug concentration in cells and could cause a decreased rate of transfer. A second possibility reported is the effect on the extracellular or pore route of drug diffusion across membranes. As the cells swell due to fluid uptake, there is a concomitant decrease in the effective pore or channel diameter. If this is the case, the degree of inhibition of drug transfer caused by cellular swelling should be dependent upon this absorption pathway. The effect of sugars such as glucose or sucrose on absorption would be expected to vary with the drug. The greater effect of glucose on the decrease in passive transfer of riboflavin compared to sulphanilamide or salicylate lends support to this proposed mechanism (Mayersohn and Gibaldi, 1971).

The primary purpose of this investigation was to determine if sorbitol solution can modify the absorption of theophylline. Theophylline is well absorbed throughout the gastrointestinal tract and is also stable within this organ system. Sorbitol, a slowly and incompletely absorbed sugar alcohol, is widely used as a sweetener in the manufacture of food and drinks, and is a major component of many proprietary pharmaceutical syrup formulations. Diabetic patients may, in fact, ingest up to 30 g daily (Martindale, 1979). Five 22–24-year-old healthy, non-smoking, and informed adult male volunteers participated in the crossover study. Each subject gave written consent to participate in the study. Xanthine-containing beverages, other medication or alcohol, were disallowed 72 h prior to and throughout the entire study. Theophylline kinetics were studied in each subject, once following ingestion of an aminophylline tablet (200 mg) with 240 ml water, and once with an equal amount of water containing 10 g of sorbitol. The aminophylline was administered after subjects had fasted overnight, with a 2 week wash out period between each trial. The study protocol was approved by the University Committee on Ethics and Safety. Blood samples were drawn at predetermined intervals throughout the trial (0.0, 0.25, 0.50, 0.75, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 6.0, 8.0, 10, 12 and 24 h), centrifuged, and the serum separated and frozen until analysed by fluorescence polarization immunoassay. The pharmacokinetic parameters C_{max} and t_{max} were extracted strictly from observed data, where $AUC_{0-\infty}$, k_{el} and $t_{1/2}$ were calculated by the trapezoidal rule with extrapolation to infinity using the terminal slope of the serum concentration-time curve, which was determined by linear regression analysis (Al-

TABLE 1

Bioavailability parameters of theophylline after administration with water (W) and sorbitol (S)

Subject	C_{max}		t_{max}		$AUC_{0-\infty}$		K_{el}		$t_{1/2}$	
	W	S	W	S	W	S	W	S	W	S
1	5.82	5.76	1.25	2.0	78.32	83.24	0.0824	0.0688	8.4	10.1
2	4.82	4.21	1.50	4.0	98.43	103.24	0.0546	0.0472	12.7	14.7
3	4.73	5.96	1.25	1.5	77.74	88.81	0.0689	0.0593	10.1	11.7
4	4.84	5.13	0.5	1.0	82.50	86.73	0.0442	0.0431	15.7	16.1
5	4.85	5.27	2.0	2.0	67.59	69.14	0.0795	0.0631	8.7	11.0
Mean	5.01	5.27	1.30	2.10	80.92	86.23	0.0659	0.0563	11.1	12.7
±SD	0.45	0.68	0.54	1.14	11.22	12.22	0.0163	0.0108	3.1	2.6

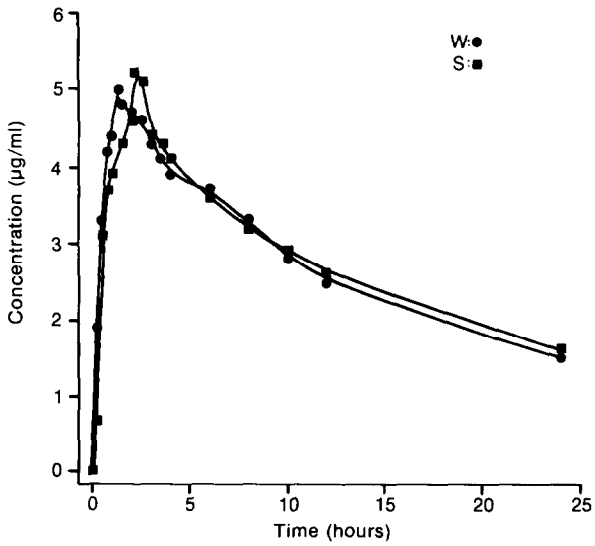

Fig. 1. Theophylline serum concentration profiles (mean of 5 determination) after administration of tablets with water (W) and sorbitol solution (S).

len et al., 1982; Gibaldi and Perrier, 1982). The pharmacokinetic parameters are summarised in Table 1 and the mean serum theophylline concentration versus time profiles are shown in Fig. 1. Individual variations in the rate of drug absorption from any dosage form may be due largely to differences in the rate of gastric emptying (Heading et al., 1973). Many drugs are not absorbed significantly until they reach the small intestine, and since intestinal absorption is often a rapid process we sometimes find that gastric emptying rather than permeation is the rate-limiting step in gastrointestinal drug absorption. Heading et al. (1973) observed highly significant correlations between gastric emptying half-life in convalescent hospital patients and the time to maximum plasma concentration of paracetamol after an oral dose. In general, aqueous diffusion is a pathway of limited capacity across most barrier, e.g. the epithelial lining of the surfaces of the body, such as the gut, and bladder. Because the epithelial cells in these tissues are connected by tight junctions, only molecules small enough (less than MW 200) to pass through very small aqueous pores permeate these barriers by the aqueous route. However, movement across cell membranes by solution in the lipids of the membrane, with passive transfer across the lipid driven by a concentration gradient, is one of the most important mechanisms of drug permeation. Theophylline has small molecular size (MW 180), pK_a of 8.8 with more than one ionizable group and low partition coefficient (log P (octanol), -0.8) and is completely absorbed throughout the GIT. This suggests that lipid diffusion, facilitated diffusion and pinocytosis do not play a major role in theophylline absorption and that the paracellular pathway could play a role in the absorption of this drug.

The available data from the present study indicate that the drug is essentially completely absorbed from the test solution administered with the oral dosage form of theophylline. However, the absorption rate is probably the more important therapeutic parameter when rapid onset of drug effect is desirable. Differences in rate of availability may become important for drugs given as a single dose, such as hypnotic drugs used to induce sleep, analgesics to relieve pain or those drugs designed especially to be released and absorbed continuously (e.g. sustained release theophyllines and other slow release preparations). As discussed, differences between individuals and individual stomach emptying times can dominate over formulation variables. A maximum absorption rate with peak levels prior to 1.30 h appears to be obtained when theophylline is taken with water following fasting. Dosing with sorbitol solution, however, increased the time for attainment of the maximum plasma concentration to 2.10 h (see Fig. 2). The difference between these values is statistically significant ($p < 0.05$). The delayed attainment of t_{max} may be explained by both a reduced gastric emptying rate or retardation of the flux of drug across the gastric mucosa. It is important to note that transcellular transport across the enterocyte involves uptake from the gut across the brush-border membranes, diffusion through the cytoplasm, and exit to the blood across the basolateral membranes. In general, the transport across the brush-border membranes is regarded as the most important step for the intestinal absorption of drugs. Reasons have been given for believing that the lateral intercellular spaces of the duodenal enterocytes act as the transducer for the

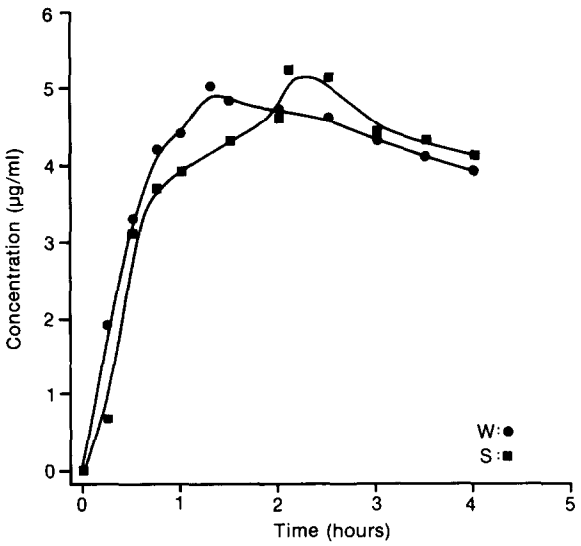

Fig. 2. Actual t_{max} values and absorption profiles during the first 4 h (enlarged from Fig. 1) following administration of theophylline with water (W) and sorbitol solution (S).

slowing of gastric emptying by the osmotic effects of the products of digestion and some solutions (Barker et al., 1978).

It was proposed that minimal inhibition of gastric emptying, for example, with 120 mM NaCl (Hunt, 1956), corresponds to maximal dimensions of the lateral intercellular space (Tomasini and Dobbins, 1970). Osmotic stimuli that slow gastric emptying (Hunt and Knox, 1971), for example, mannitol, more than 75% confined in the lumen (Saunders and Wiggins, 1981), could do so by shrinking the lateral intercellular spaces (McElligott et al., 1975). It has also been proposed (Barker et al., 1978) that osmotic stimuli in the duodenal lumen slow gastric emptying by reducing the flux of water into the space between the enterocytes on the duodenal villi. This shrinks the space. The shrinking of the space sets up a signal that is carried either by vagal afferent fibres (Leek, 1977) and/or by hormones (Tomasini and Dobbins, 1970; Valenzuela and Defilippi, 1981). This signal causes the slowing of gastric emptying.

Speculatively, it may be suggested that the increase in t_{max} value in this study may be thought of as shrinking of the lateral spaces of the duodenal enterocytes by sorbitol solution which changes fluxes of water in and out of lateral intercellular spaces, a factor that mediates the slowing of gastric emptying.

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