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Effect of dietary cellulose on the absorption and bioavailability of theophylline

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In the past few decades, the number of studies on dietary fibre has increased rapidly since epidemiologic evidence has related low fibre intake to a greater incidence of colon and rectum cancer (Burkitt, 1971), diverticulosis (Painter and Burkitt, 1971; Painter and Burkitt, 1975), ischaemic heart disease (Trowell, 1972), diabetes and haemorrhoids (Tasman-Jones, 1976). There are claims that addition of fibre to the diet can prevent these health problems. As a result, the popularity of fibre has grown among the general public, but there is also evidence that certain dietary fibres may adversely affect the digestion and absorption of other nutrients as well as the bioavailability of drugs. For example, pectin, found in apples and pears, can retard the absorption of acetaminophen and retard or decrease the absorption of digoxin (Roe, 1981; Hansten, 1985). These effects have been attributed to an increased thickness or resistance of the unstirred water layer barrier, at the intestinal surface, to nutrient and drug absorption. Dietary fibres may acutely interfere with bulk phase diffusion of drugs in the intestinal lumen or alter the transport characteristics of drug molecules at the mucosal surface.

Dietary fibre is a complex mixture of cellulose, hemi-celluloses, pectic substances and other associated components varying in their chemical and physical properties and exerting diverse physiological effects.

From current knowledge of the physiological responses to fibre-rich foods, and to individual types of fibre components, several potentially important mechanisms may be suggested by which fibres can alter the rate and/or extent of drug absorption. These include, among others: rates of gastric emptying; altered pH and metabolic responses in the stomach; effects on intestinal motility and transit; modification of digestive enzyme activities; sequestration of lipid micellar components, and interaction of fibre with the intestinal surface (Vahouny and Cassidy, 1985). Nutrient–drug interactions appear to be primarily an adsorption phenomenon, and are influenced by pH and osmolarity, bile acid structure, and the physical and chemical forms of the fibre (Eastwood and Hamilton, 1968). Thus, diet and nutrition can have a profound effect on the therapeutic or toxic outcome of drug treatment. Not every drug interacts with a nutrient to induce a clinically significant effect. However, risk factors disposing to drug–nutrient interactions include: multiple drug treatments, chronic drug therapy, nutritionally marginal diets, and age- or disease-related malab-

sorption disorders (Blumberg, 1986). The influence of food on theophylline absorption after administration of slow release formulations has been extensively investigated, but results are inconsistent. Thus food has been found to decrease both the rate and extent of absorption (Leeds et al., 1982; Osman et al., 1983; Thompson et al., 1983; Pedersen, 1981), increase both rate and extent of absorption (Hendeles et al., 1984, 1985; Karim et al., 1985; Vaughan et al., 1984), or to have no effect on either (Thebault et al., 1987).

As part of an ongoing study we investigated the possible effects of non-soluble fibre on the rate and extent of absorption of theophylline administered in an immediate-release dosage form as opposed to slow-release forms. The latter preparations are subject to a wider variety of circumstances during their extended time in the gastrointestinal tract, and are thus not ideal for the investigation of fibre effects per se.

A suspension of non-soluble cellulose (microcrystalline cellulose, purchased from FMC corporation, Philadelphia, P.A.) in 240 ml of water was prepared. Four informed, 22–24-year-old healthy male volunteers participated in the study. No xanthine-containing beverage was allowed from 48 h before the trial. Theophylline kinetics were studied in a randomized cross-over design at intervals of two weeks following ingestion of two 100 mg aminophylline tablets with 240 ml water (control), and also with an equal amount of water containing 15 grams of non-soluble fibres. The study protocol was approved by the University Committee on Ethics and Safety. Blood samples were drawn at predetermined intervals throughout the trial, centrifuged, and the serum separated and frozen until analysed by fluorescence polarization immunoassay (TDX-analyser system, Abbott Laboratories). The bioavailability parameters C_{max}, t_{max}, AUC_{0-24}, K_{el} and $t_{1/2}$ were calculated.

The bioavailability of drugs is significantly influenced by diet and nutritional status. Theophylline has a very narrow therapeutic range. Changes in its pharmacokinetics brought about by different eating patterns can have important clinical consequences, as they may increase the risk of under- or overdose. Traditionally, drug–nutrient interactions have been grouped under four headings (Roe, 1981): (i) The effect of diet on the absorption, distribution and elimination of drugs; (ii) drug–nutrient incompatibilities; (iii) drug bioavailability in malnourished subjects and (iv) drug-induced changes in nutritional status.

Results of the present investigation indicate that there is no significant drug–cellulose interaction. The rate and extent of theophylline absorption in all subjects was very similar after administration with and without cellulose fibres. The mean theophylline serum concentration–time curves obtained are presented in Fig. 1. The mean peak theophylline serum concentration following coadministration with cellulose fibres was 5.30 μg/ml

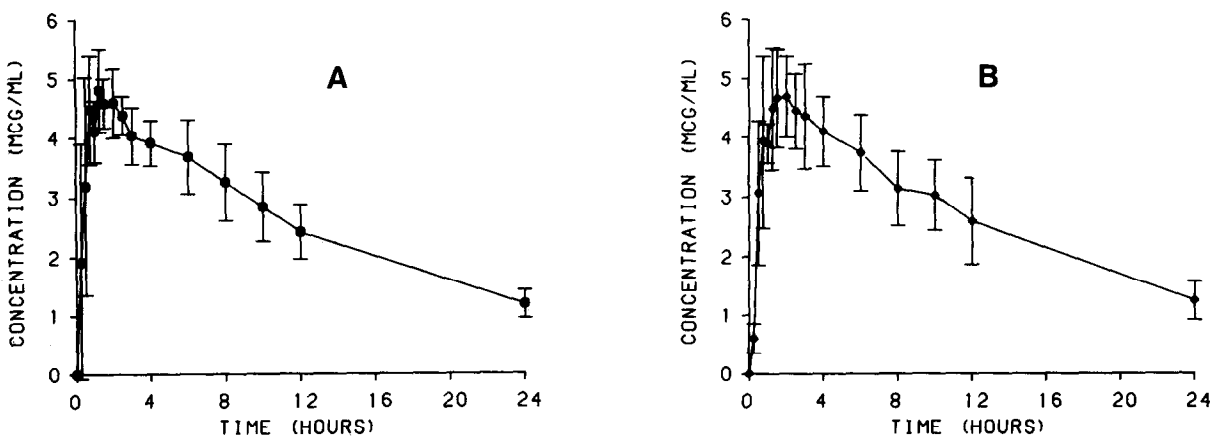

Fig. 1. Theophylline serum concentrations (mean ±S.D.) after administration of tablets with water (A) and suspension of cellulose (B).

TABLE 1

Bioavailability parameters of theophylline when administered with water (W) and with cellulose (C)

Subject	C_{max} (μg/ml)		t_{max} (h)		AUC_0^{24} (μg/ml · h)		K_{el} (h^{-1})		$t_{1/2}$ (h)	
	W	C	W	C	W	C	W	C	W	C
1	5.82	5.53	1.25	1.50	65.58	73.52	0.0824	0.0680	8.4	10.2
2	4.82	5.03	1.50	2.50	70.93	73.93	0.0546	0.0494	12.7	14.0
3	4.73	5.68	1.25	1.25	59.60	57.05	0.0689	0.0696	10.1	10.0
4	4.85	4.97	0.50	0.75	53.09	51.78	0.0442	0.0563	15.7	12.3

The mean ± S.D. of AUD_{0-24} values following administration with water (62.30 ± 7.69) and cellulose (64.07 ± 11.36) were not statistically significant ($P > 0.05$).

and was very similar to that observed with water, viz. 5.06 μg/ml. Peak serum theophylline levels were achieved within 1.13 to 1.50 h for both treatments. The mean values of the areas under serum concentration–time curves and other bioavailability parameters are shown in Table 1. The C_{max} values obtained did not differ significantly after dosing with water or with the suspension of cellulose. Similarly, the differences for t_{max} values were statistically not significant, as show in Fig. 2.

It is clear from the above evidence that the rate and extent of theophylline absorption is very similar after administration with water and with cellulose. Theophylline was rapidly absorbed with sharp peak concentrations reached, in most cases, within 1.5 h after dosing. It would appear that, with regard to dietary fibre, in general, it is not necessary to recommend any special precautions when theophylline is prescribed.

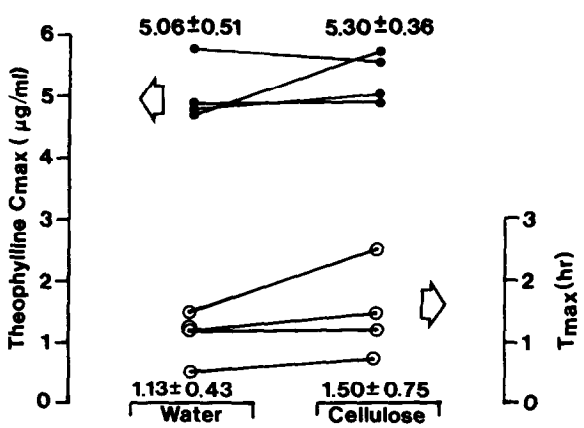

Fig. 2. Actual peak theophylline concentration (C_{max}) and t_{max} values following administration with water and suspension of cellulose (individual points and mean ± S.D. values). No significant differences exist ($p > 0.05$).

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