Effects of a non-absorbable osmotic load on drug absorption in healthy volunteers

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- 1 We have studied the effects of a non-absorbable osmotic load on the absorption of a multicomponent solution of frusemide, atenolol, hydrochlorothiazide and salicylic acid in six healthy volunteers.
- 2 Each subject was studied on up to four separate occasions. The drugs were administered in one of four solutions: a) a mannitol/electrolyte solution, b) a double-strength mannitol/electrolyte solution, c) a glucose/electrolyte solution and d) water. Lactulose or sulphasalazine were added as oro-caecal transit markers. Lactulose was included in the mannitol- and glucose-based solutions, adding a further non-absorbable osmotic load, and sulphasalazine was added to the water, adding little osmotic load.
- 3 The absorption of atenolol and hydrochlorothiazide was two- to three-times less from all lactulose-containing solutions than from the sulphasalazine-containing solution. The absorption of frusemide and salicylic acid was similar from all four solutions.
- 4 The largest non-absorbable osmotic load impaired the absorption of atenolol and hydrochlorothiazide most and the incorporation of glucose only partly restored absorption.
- 5 These results suggest that transmucosal water movement is an important determinant of atenolol and hydrochlorothiazide absorption but is less relevant for the absorption of frusemide and salicylic acid. Furthermore, these data demonstrate a previously unrecognised interaction between a commonly prescribed laxative – lactulose, and atenolol and hydrochlorothiazide.

Keywords osmotic effects drug absorption lactulose mannitol glucose
atenolol hydrochlorothiazide frusemide salicylic acid

Introduction

Intestinal perfusion studies in animals suggest that transmucosal water flux is an important determinant of drug absorption. For a range of acidic and basic drugs, absorption appears enhanced by water absorption and impaired by water secretion (Ochsenfahrt & Winne, 1974a,b). The relevance of these findings to oral drug absorption in man has not been explored.

The magnitude of transmucosal water flux in human intestine is considerable (Phillips, 1972). In addition to the two litres of fluid ingested in the diet, approximately six litres of salivary, gastric, biliary and pancreatic secretions enter the duodenum each day. In addition, the small intestinal mucosa actively secretes in response to meals (Powell, 1987) and passive water secretion also occurs if the intestinal contents are hypertonic (Ladas *et al.*, 1983; Miller *et al.*, 1978).

Approximately 99% of this ingested and secreted

water load is absorbed; 44% in the duodenum and jejunum, 39% in the ileum and a final 16% in the colon (Phillips, 1972; Phillips & Giller, 1973). Water absorption is not an active process but occurs as a consequence of solute absorption. In the jejunum nutrient absorption provides the major driving force for water absorption whereas in the ileum active ion transport is largely responsible (Turnberg, 1987). Such forces may be opposed, however, by the osmotic pressure derived from non-absorbable solutes that remain within the intestinal lumen.

In a companion study we included lactulose in an oral test solution to assess the influence of oro-caecal transit on drug absorption and found an unexpectedly low absorption of drugs from this solution. Since lactulose passes through the small intestine largely unchanged, its osmotic effect may have reduced water absorption and

thereby impaired drug absorption. We have therefore studied the absorption of these drugs from solutions of varying osmotic load.

Methods

Subjects

Six healthy volunteers were studied, ages ranged from 19 to 22 years. All were in good health and had no significant gastrointestinal symptoms. No subject had a history of gastrointestinal surgery or known allergy to the study drugs and all were asked to abstain from medications and alcohol throughout the study period. The protocol was approved by Hope Hospital Ethics Committee and subjects gave written informed consent prior to study.

Study protocol

Each subject was studied on three or four separate occasions, at intervals of at least 1 week. On each occasion the same four study drugs: frusemide 20 mg, atenolol 25 mg, hydrochlorothiazide 25 mg and salicylic acid 500 mg, were administered in a 200 ml multicomponent test solution. The composition of this solution was varied on different study days in order to manipulate trans-mucosal water movement (Table 1).

Solution A was a mannitol/electrolyte solution, initially developed as an orally administered colonic lavage solution since it passes through the gut largely unchanged (Davis *et al.*, 1980). Solution B contained the same constituents as solution A but at twice the concentration, to stimulate intestinal water secretion, and solution C contained a high concentration of glucose, to stimulate water absorption (Alpers, 1987). Lactulose was incorporated into solutions A, B and C, adding a further non-absorbable osmotic load and enabling measurement of oro-caecal transit time. Solution D was tap water, to which was added sulphasalazine as a marker of oro-caecal transit (Kellow *et al.*, 1986). As sulphasalazine has poor aqueous solubility the drug was added to the test solution as a suspension (2 g in 200 ml), adding little to the osmotic load.

Each study followed a standard protocol. After an

overnight fast, baseline samples of blood and urine were taken. At 10.00 h the 200 ml multicomponent test solution was sipped quickly, through a straw. Subjects remained sedentary throughout the study and blood samples were drawn, from an indwelling intravenous cannula, at 10, 20, 30, 45, 60 and 90 min and at 2, 3, 4, 5, 6, 9, 12 and 24 h after ingestion of the test solution. All urine was collected during the 24 h period following drug ingestion and aliquots of plasma and urine were stored at -20°C prior to analysis. Subjects were allowed water after 4 h and resumed normal dietary intake 6 h after ingestion of the test solution.

Oro-caecal transit measurement

Oro-caecal transit times were measured using the lactulose-breath hydrogen method and the sulphasalazine-plasma sulphapyridine technique.

Lactulose passes unchanged through the stomach and small intestine but on reaching the caecum it is metabolised by faecal flora with the production of hydrogen. A rise in breath hydrogen following lactulose ingestion is, therefore, a useful measure of oro-caecal transit time (Bond *et al.*, 1975). Breath hydrogen levels were measured before ingestion of lactulose-containing test solutions (A, B and C), then at 5 min intervals for 2 h and at 10 min intervals for a further 4 h, as detailed previously (Riley *et al.*, 1991).

Sulphasalazine also passes through the stomach and small intestine unchanged. On reaching the caecum, bacterial azoreductase enzymes cleave the drug into its component parts: 5-aminosalicylic acid and sulphapyridine. The sulphapyridine component is rapidly absorbed and passes into the systemic circulation. The appearance of sulphapyridine in the plasma following the ingestion of sulphasalazine is, therefore, an alternative measure of oro-caecal transit time (Kellow *et al.*, 1986).

Plasma sulphapyridine concentrations were measured before and after ingestion of test solution containing sulphasalazine (solution D). Blood samples (2 ml) were drawn at 10 min intervals for 6 h and then at 9, 12 and 24 h. Plasma sulphapyridine concentrations were measured using a modification of the method of Bratton and Marshall (Kellow *et al.*, 1986). Plasma samples (0.5 ml) were precipitated with 15% w/v trichloroacetic acid (4 ml) and centrifuged at 2000 rev min^{-1} for 5 min. Following the sequential addition of 0.1% w/v sodium nitrite (0.5 ml), w/v 0.5% ammonium sulphamate (0.5 ml) and 0.1% w/v *N*-1-naphthylethylenediamine dihydrochloride (0.5 ml) the absorbance of the supernatant was measured at 545 nm. Oro-caecal transit of the head of the test solution was defined at the time to first appearance of sulphapyridine in the plasma.

Drug analysis

Plasma and urinary frusemide, atenolol, hydrochlorothiazide and salicylic acid concentrations were measured as detailed previously (Riley *et al.*, 1991).

Statistical analysis

All results are expressed as mean $\pm$ s.d. unless otherwise stated. Analysis of variance was used to study the differ-

Table 1 Composition of the four test solutions

	A	B	C	D
Na^+ (meq l^{-1})	125	250	65	—
K^+ (meq l^{-1})	10	20	10	—
Cl^- (meq l^{-1})	35	70	35	—
HCO_3^- (meq l^{-1})	20	40	20	—
SO_4^{2-} (meq l^{-1})	40	80	10	—
Glucose (mmol l^{-1})	—	—	170	—
Mannitol (mmol l^{-1})	80	160	—	—
PEG (g l^{-1})	5	10	5	—
Lactulose (g 200 ml^{-1})	10	10	10	—
Sulphasalazine (g 200 ml^{-1})	—	—	—	2
Osmolarity (mOsm l^{-1})	486 ± 16	761 ± 21	516 ± 12	24 ± 9

ences in oro-caecal transit and drug absorption from the four different solutions.

Results

The results of oro-caecal transit measurements following ingestion of the four test solutions are shown in Figure 1. Following ingestion of solutions A, B and C the times to first rise in breath hydrogen concentrations were 50.0 ± 9.3 , 50.0 ± 14.5 , and 54.0 ± 14.7 min respectively. These differences were not statistically significant. Following ingestion of solution D, however, the time to first appearance of plasma sulphapyridine was 172 ± 27.7 min ($P < 0.005$ compared with solutions A, B and C).

Figure 2 shows the results of 24 h urinary atenolol excretion from the four test solutions. The excretion of atenolol from solution D was 8.34 ± 2.42 mg ($33.3 \pm 9.7\%$ of the ingested dose). Atenolol excretion following solutions A, B and C, however, was considerably less ($P < 0.001$). Furthermore, drug excretion from the glucose-electrolyte solution (solution C = 3.32 ± 0.46 mg) was greater than from mannitol/electrolyte solution (solution A = 2.68 ± 0.25 mg) which was, in turn, greater than from the double-strength mannitol/electrolyte solution (solution B = 1.87 ± 0.43 mg, $P < 0.05$ compared with solution C). Parallel changes were seen when the areas under the plasma concentration-time curves (AUC) and the peak plasma concentrations ($C_{\max}$) were compared. The time to peak atenolol concentration ($t_{\max}$), however, was unaffected by the type of solution ingested (Table 2).

Figure 1 Oro-caecal transit of the four test solutions. The oro-caecal transit times of the three lactulose-containing solutions (A, B and C) were not significantly different but all were three times more rapid than the transit of the solution containing sulphasalazine (D), $P < 0.005$.

Figure 2 The 24 h urinary excretion of atenolol following ingestion of the four test solutions. Excretion was considerably less from all lactulose-containing solutions (A, B and C) than from the sulphasalazine-containing solution (D). Furthermore, excretion from the glucose-based solution (C) was greater than from the mannitol/electrolyte solution (A), $P < 0.01$, which was, in turn, greater than excretion from the double-strength mannitol/electrolyte solution (B), $P < 0.005$.

The results of 24 h urinary hydrochlorothiazide excretion are shown in Figure 3. The pattern of excretion following ingestion of the four solutions was similar to that seen with atenolol. Hydrochlorothiazide excretion was 8.78 ± 2.50 mg from solution D ($35.1 \pm 10.0\%$ of the ingested dose), 3.19 ± 0.56 mg from solution C ($P < 0.001$ compared to solution D), 2.14 ± 0.21 mg from solution B ($P < 0.05$ compared with solution C), and 2.77 ± 0.45 mg from solution A. Parallel changes in hydrochlorothiazide AUC and $C_{\max}$ values were seen but the time to peak plasma hydrochlorothiazide concentration was again unaffected (Table 2).

The 24 h urinary excretion of frusemide and salicylic acid is shown in Figures 4 and 5. Solution composition had no significant effect on the urinary excretion of either drug (Frusemide: solution A = 4.12 ± 1.40 mg, solution B = 4.62 ± 1.29 mg, solution C = 4.16 ± 1.24 mg, solution D = 5.81 ± 2.18 mg; Salicylic acid: solution A = 379 ± 56 mg, solution B = 379 ± 50 mg, solution C = 397 ± 70 mg, solution D = 437 ± 55 mg). Frusemide AUC, $C_{\max}$ and $t_{\max}$ values were also similar. Salicylic acid AUC values, however, were slightly greater with solution D but $C_{\max}$ and $t_{\max}$ were unchanged (Table 2).

Discussion

The four test solutions used in this study were designed to manipulate transmucosal water movement. In a companion study we had found reduced atenolol and

Figure 3 The 24 h urinary hydrochlorothiazide excretion following ingestion of the four test solutions. Excretion was considerably less from all lactulose-containing solutions (A, B and C) than from the sulphasalazine-containing solution (D). Furthermore, excretion from the glucose-based solution (C) was greater than from the mannitol/electrolyte solution (A), $P = 0.06$, which was, in turn, greater than excretion from the double-strength mannitol/electrolyte solution (B), $P < 0.02$.

hydrochlorothiazide absorption when the drugs were administered in an isotonic solution containing lactulose as a non-absorbable osmotic load. In the present study solutions A, B and C contained lactulose but, in addition, were made hypertonic. Solutions A and B were made hypertonic by a further non-absorbable mannitol/electrolyte load, solution B having twice the load of solution A, and solution C was made hypertonic by the

Figure 4 No significant differences were observed in the 24 h urinary excretion of frusemide following ingestion of the four test solutions.

Table 2 Measures of drug absorption from the four test solutions

	A	B	C	D
<i>Frusemide</i>				
$C_{\max}$ (ng ml ⁻¹)	275 ± 68.7	228 ± 91.3	270 ± 68.1	575 ± 226
$t_{\max}$ (min)	55.0 ± 7.7	60.0 ± 0	60.0 ± 18.4	51.0 ± 22.7
AUC (mg l ⁻¹ h)	0.597 ± 0.168	0.507 ± 0.243	0.502 ± 0.149	0.965 ± 0.577
24 h urine excretion (% of ingested dose)	20.6 ± 7.0	23.1 ± 6.4	20.8 ± 6.2	29.0 ± 10.9
<i>Atenolol</i>				
$C_{\max}$ (ng ml ⁻¹)	27.3 ± 6.2	21.3 ± 8.0	41.3 ± 9.5	184 ± 53.6
$t_{\max}$ (min)	110 ± 41.0	144 ± 68.4	120 ± 70.4	186 ± 105
AUC (mg l ⁻¹ h)	0.363 ± 0.101	0.223 ± 0.091	0.497 ± 0.054	1.721 ± 0.437
24 h urine excretion (% of ingested dose)	10.7 ± 1.0	7.5 ± 1.7	13.3 ± 1.8	33.3 ± 9.7
<i>Hydrochlorothiazide</i>				
$C_{\max}$ (ng ml ⁻¹)	65.6 ± 15.6	47.8 ± 21.5	101 ± 48.5	221 ± 71.5
$t_{\max}$ (min)	115 ± 35.1	138 ± 91.5	108 ± 26.8	168 ± 26.8
AUC (mg l ⁻¹ h)	0.487 ± 0.094	0.387 ± 0.195	0.570 ± 0.127	1.313 ± 0.043
24 h urine excretion (% of ingested dose)	11.1 ± 1.8	8.5 ± 0.8	12.7 ± 2.2	35.1 ± 10.0
<i>Salicylic acid</i>				
$C_{\max}$ (µg ml ⁻¹)	53.0 ± 5.9	53.7 ± 5.7	52.5 ± 6.2	51.6 ± 10.5
$t_{\max}$ (min)	52.5 ± 12.5	60.0 ± 0.0	51.0 ± 13.4	60.0 ± 35.2
AUC (mg l ⁻¹ h)	333 ± 52.7	315 ± 58.7	327 ± 51.7	392 ± 73.3
24 h urine excretion (% of ingested dose)	75.8 ± 11	75.8 ± 10	79.4 ± 14	87.4 ± 11

Figure 5 No significant differences were observed in the 24 h urinary excretion of salicylic acid following ingestion of the four test solutions.

addition of a high concentration of glucose. Solutions A and B were designed to induce passive water secretion and then oppose water absorption. Solution C was also hypertonic and would therefore induce passive water secretion. Glucose within the solution would then be avidly absorbed across the intestinal mucosa (Alpers, 1987) and this would be accompanied by water absorption. This movement of water, however, would be opposed by the osmotic effect of lactulose also present in the solution. Solution D was the only hypotonic solution. It contained sulphasalazine as an oro-caecal transit marker which, because of its poor aqueous solubility, imparts little osmotic load. Solution D was designed to mimic the effects of drug ingestion with water.

The drugs used in this study are all in common clinical use and are frequently prescribed in combination. There is no evidence of drug interactions within the group and atenolol, hydrochlorothiazide and frusemide are eliminated largely unchanged in the urine so that cumulative urinary excretion may be used as an index of extent of absorption (Beerman & Groschinsky-Grind, 1977; Mason *et al.*, 1979; Waller *et al.*, 1985). Although salicylic acid is extensively metabolised, total urinary salicylate is a quantitative measure of the amount of salicylic acid absorbed (Needs & Brooks, 1985).

It is well recognised that the absorption of atenolol, hydrochlorothiazide and frusemide is incomplete and demonstrates marked intra-subject variability. Previous studies report urinary recoveries of: 15–86% for atenolol, 33–84% for hydrochlorothiazide and 20–104% for frusemide (Boles Ponto & Schoenwald, 1990; Mason *et al.*, 1979; Niemeyer *et al.*, 1983). The absorption of salicylic acid, on the other hand, is rapid and complete and the drug was included largely as a test of compliance. The drugs were administered as an aqueous multi-component solution to obviate the problems of drug dissolution and permit between-drug comparisons.

The results of this and our previous study show that the absorption of atenolol and hydrochlorothiazide is

selectively impaired by the co-administration of a non-absorbable osmotic load. The absorption of atenolol and hydrochlorothiazide was two-to three-times less from all lactulose-containing solutions than from the sulphasalazine-containing solution. The absorption of frusemide and salicylic acid, however, was similar from all four solutions. Increasing the non-absorbable osmotic load by the addition of mannitol and sulphate reduced the absorption of atenolol and hydrochlorothiazide further. The addition of glucose to a lactulose-containing solution improved absorption but absorption was still only 40% of that seen when the drugs were taken with water.

In the present study we did not measure the gastric emptying of the four test solutions directly. Major differences in gastric emptying are unlikely, however, as the absorption of salicylic acid, which appears rate-limited by gastric emptying (Riley *et al.*, 1991), was similar from all four solutions. The oro-caecal transit of the lactulose-containing solutions, however, was three times faster than the solution containing sulphasalazine. Others have also noted more rapid oro-caecal transit with the lactulose-breath hydrogen method than with the sulphasalazine-plasma sulphapyridine technique (Kennedy *et al.*, 1979; Staniforth, 1989). Furthermore, an inverse relationship exists between transit time and the amount of lactulose ingested (Bond *et al.*, 1975), suggesting that lactulose speeds the transit of solutions to which it is added. It might be suggested, then, that rapid transit impairs the absorption of drugs from these solutions. This seems unlikely, however, as the amount of atenolol absorbed from the glucose-containing solution was twice that absorbed from the double-strength mannitol/electrolyte solution, yet the transit of the two solutions was identical. Moreover, the administration of codeine phosphate prior to ingestion of a lactulose-containing test solution causes a two-fold delay in transit but leaves the absorption of atenolol and hydrochlorothiazide unchanged (Riley *et al.*, 1991).

The underlying mechanism of impaired drug absorption from these solutions is not clear. The ingestion of hypertonic solutions induces passive water secretion into the duodenum and upper jejunum (Ladas *et al.*, 1983) and this may impede drug absorption. Furthermore, this secretion dilutes the luminal contents and therefore lowers the concentration gradient for absorption. However, our earlier observations (Riley *et al.*, 1991) were made following ingestion of isotonic non-absorbable test solutions and the degree of impairment of atenolol and hydrochlorothiazide absorption was similar to that seen in the present study. It seems likely, then, that impairment of water absorption, induced by the presence of non-absorbable, osmotically active luminal contents is more important in impeding drug absorption than the passive water secretion and luminal dilution induced by hypertonicity. Finally, a component of this effect may be related to a non-osmotically mediated lactulose-drug interaction. This possibility cannot be excluded by the present study.

A number of issues arise from this study. Firstly, the ingestion of lactulose markedly impaired the absorption of atenolol and hydrochlorothiazide. This is important as lactulose is in widespread clinical use. Drug interactions with lactulose have not been reported previously although in high doses lactulose may impair nutrient absorption

(Holgate & Read, 1983). Similar interactions with other polar drugs seem highly likely.

Secondly, it appears that small intestinal water movement is an important determinant of atenolol and hydrochlorothiazide absorption. Furthermore, it is well recognised that, even under standardised conditions, the rate of salivary, gastric, pancreatic and biliary secretions may vary widely between individuals (Bock *et al.*, 1963; Davenport, 1966; Dreiling & Janowitz, 1959; Mason & Chisholm, 1975; Waitman, 1969). As this secreted load is reabsorbed across the intestinal mucosa, transmucosal water absorption will also vary widely and this may account for some of the considerable inter-subject differences in the extent of atenolol and hydrochlorothiazide absorption (Mason *et al.*, 1979; Niemeyer *et al.*, 1983).

Finally, these findings point to a previously unrecognised mechanism in drug-food interactions. Drug ingestion is often linked to meal times to improve compliance (Haynes *et al.*, 1976) but by doing so the absorption of some drugs is enhanced while that of others is impaired (Winstanley & Orme, 1989). In most

cases the mechanisms of drug-food interactions are poorly understood and the effect of meal composition on drug absorption has received little attention. In this study the presence of lactulose in the test solution impaired drug absorption and this was only partly reversed by the addition of glucose. Ingestion of other non-absorbable carbohydrates, occurring naturally in foods or added as sugar substitutes (Charney & Bodurtha, 1981; Gryboski, 1966; Hickey *et al.*, 1972), may therefore impair the absorption of certain drugs. The ingestion of glucose and other actively transported nutrients, on the other hand, may stimulate drug absorption. Following ingestion of a complex meal, the overall effect on drug absorption would depend on meal composition, its state of digestion, and the susceptibility of the drug to such changes. Further studies with different drugs and varied test solutions and meals would be of interest.

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