The influence of gastrointestinal transit on drug absorption in healthy volunteers

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- 1 The effect of variability of gastric emptying and oro-caecal transit on the absorption of a multicomponent solution of frusemide, atenolol, hydrochlorthiazide and salicylic acid has been studied in six healthy subjects. Each subject was studied on five separate occasions: three times under basal conditions, once following metoclopramide and once following codeine pretreatment in an attempt to speed and slow transit respectively.
- 2 Inter-subject variability of gastric emptying, oro-caecal transit and the rate and extent of drug absorption was considerable.
- 3 The absorption of salicylic acid appeared rate-limited by gastric emptying but the rate and extent of frusemide, atenolol and hydrochlorthiazide absorption were unrelated to measures of gastric emptying or oro-caecal transit.
- 4 Codeine phosphate caused a two-fold delay in oro-caecal transit but did not influence gastric emptying while metoclopramide had no significant effect on either function.
- 5 Metoclopramide and codeine had no significant effect on the rate or extent of absorption of any of the study drugs.
- 6 Within the limits of this experiment, oro-caecal transit time did not appear to be an important determinant of frusemide, atenolol, hydrochlorothiazide or salicylic acid absorption. Other factors must account for the observed variability in drug absorption.

Keywords gastric emptying oro-caecal transit variability drug absorption
frusemide atenolol hydrochlorothiazide salicylic acid metoclopramide
codeine

Introduction

Drug absorption from the gastrointestinal tract is a complex process subject to many variables. The physico-chemical characteristics of a drug and its pharmaceutical formulation are key determinants and these have been studied extensively. However, relatively little is known of the physiological factors that influence the absorptive process.

In recent years there has been a growing awareness of inter- and intra-subject variability in both the rate and extent of oral drug absorption (Grahnen *et al.*, 1984; Kochak *et al.*, 1989; Shim & Hong, 1989). The causes of such variability are poorly understood but physiological factors, operating within the gastrointestinal tract, may be responsible.

The small intestine is generally regarded as the main site of drug absorption in man. The stomach and colon contribute much less to the extent of absorption of orally administered compounds. Gastric emptying, however, may have a marked effect on the rate of drug absorption,

since it governs access to the main absorptive surface. This relationship is particularly well seen with drugs that are rapidly absorbed as gastric emptying becomes rate-limiting (Clements *et al.*, 1978).

It is widely acknowledged that the extent of gastrointestinal drug absorption is related to contact time with the small intestinal mucosa (Csaky, 1984; Hirtz, 1985; Levine, 1970). Thus small intestinal transit time may be an important determinant of absorption especially if drugs are incompletely absorbed. Studies in healthy volunteers have shown considerable variability in oro-caecal transit time when measured using the lactulose-breath hydrogen technique (La Brooy *et al.*, 1983). As the absorption of polar drugs tends to be both variable and incomplete we have studied the relationships between gastrointestinal transit and the absorption of three commonly prescribed polar drugs. The absorption of salicylic acid, a small, well absorbed drug was studied simultaneously.

Methods

Subjects

Six subjects were studied, three male and three female, with ages ranging from 23 to 45 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 five separate occasions, at intervals of at least 1 week. On each occasion simultaneous measurements of gastric emptying, oro-caecal transit and drug absorption were made following the ingestion of a multicomponent solution of the four study drugs. Three basal studies were performed following a standard protocol, to allow assessment of inter- and intra-subject variability. In the remaining two studies oral metoclopramide 20 mg or codeine phosphate 60 mg were administered 60 min before the test solution to study effects of speeding and slowing small intestinal transit (Bateman *et al.*, 1980; Findlay *et al.*, 1977; Holgate & Read, 1985; O'Brien *et al.*, 1988).

After an overnight fast, baseline samples of blood and urine were taken. Subjects were then positioned on a couch, with the back-rest angled at 45°. At 10.00 h a 200 ml multicomponent test solution was sipped quickly, through a straw. The solution comprised: i) the four study drugs—frusemide 20 mg, atenolol 25 mg, hydrochlorothiazide 25 mg, and salicylic acid 500 mg, ii) a non-absorbable radioisotope-technetium hepatate 1.5 MBq, to allow measurement of gastric emptying by external counting (Ostick *et al.*, 1976), and iii) a non-absorbable disaccharide—lactulose 10 g, to allow assessment of oro-caecal transit by breath hydrogen monitoring. 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). Solutions were approximately isotonic (271 ± 8 mOsm l^{-1}) and within the pH range 7.45 to 7.55.

Blood samples were drawn, from an indwelling intra-venous canula, 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 $-20^{\circ}C$ prior to analysis. Subjects were allowed water after 4 h and resumed normal dietary intake 6 h after ingestion of the solution.

Gastric emptying and oro-caecal transit measurements

Radioactivity from the technetium-labelled solution was measured using a single crystal scintillation detector connected to a counter ratemeter. This method has been shown to give as good an index of gastric emptying as

gamma camera scintigraphy and requires only a fraction of the radiation dose (Ostick *et al.*, 1976). Before the study the detector was positioned over the left side of the epigastrium and a background count was taken. Immediately after ingestion, optimal positioning of the detector over the area of maximal activity was achieved using the ratemeter display. The first timed count began 2 min after ingestion and counts were taken for 50 s every 2 min. Measurements were discontinued either 2 h after ingestion or when count activity had fallen to below 10% of its original value, whichever was the earlier. Background activity was subtracted from all readings and corrections were made for decay of the isotope that had occurred during the course of the study. From these data an exponential curve was derived by the method of least squares (Elashoff *et al.*, 1982). Three values were derived from this curve: i) t_{50} , the half-emptying time, the most widely used single index of gastric emptying ii) t_{20} , the time to 20% emptying, used as an index of early gastric emptying, and iii) t_{80} , the time to 80% emptying, used as an index of late gastric emptying.

Breath hydrogen levels were measured before ingestion of the test solution, then at 5 min intervals for 2 h and at 10 min intervals for a further 4 h. Before the study all subjects washed their mouths thoroughly with 1% chlorhexidine solution, in order to reduce contamination by oropharyngeal microflora. Smoking was not allowed. End-expiratory breath samples were collected into 30 ml plastic syringes via a 3-way tap. Hydrogen concentrations were measured with an electrochemical breath analyser (GMI Medical Ltd., UK) which was calibrated by room air (undetectable hydrogen) and a standard gas mixture containing 96 ppm hydrogen. All samples were analysed within 7 h of collection. Oro-caecal transit of the head of the test solution was defined as the time to the first sustained rise in breath hydrogen concentration (OCR) and the time to peak hydrogen response (OCP) was used as a measure of when all the solution had entered the colon (Read *et al.*, 1980).

Drug analysis

Plasma and urinary frusemide concentrations were measured by high performance liquid chromatography with fluorometric detection. Urine was directly chromatographed after centrifugation. Plasma samples were acidified with 5 M HCl and then extracted into ether. Samples were separated on a 5 μ m reverse-phase column (Spherisorb ODS1, 200 $\times$ 4.6 mm) using 0.1 M phosphoric acid, acetonitrile, methanol (60:35:5) mixture as eluent. Excitation and emission wavelengths were 229 nm and 395 nm, respectively (Martin *et al.*, 1984).

Measurements of plasma and urinary atenolol were also by h.p.l.c. with fluorometric detection. Urine samples were acidified with 0.1 M acetic acid prior to separation. Plasma samples were alkalised with 0.1 M NaOH and then extracted into ethyl acetate. Plasma samples were separated on 3 μ m column and urine samples on a 5 μ m reverse-phase column (Hypersil ODS, 100 $\times$ 4.6 mm). The elution mixture was methanol, water and trifluoroacetic acid (25:75:0.1 for plasma and 35:65:0.1 for urine) with 2% w/v heptane sulphonic acid.

Excitation and emission wavelengths were 235 nm and 300 nm (Taylor *et al.*, 1981).

The analysis of hydrochlorothiazide was by h.p.l.c. with ultraviolet detection. Samples were extracted into ethyl acetate and then alkalised with 0.1 M NaOH prior to injection. A 5 µm column (Hypersil ODS, 100 × 4.6 mm) was used and the eluent was acetonitrile, water and trifluoroacetic acid (15:85:0.1). Absorbance was measured at 270 nm. The limit of assay was 10 ng ml⁻¹ and within- and between-batch coefficients of variation were 1.7% and 7.0%, respectively.

Plasma salicylic acid concentrations were measured using a fluorometric assay. Samples were diluted with 0.1 M NaOH and read at an excitation wavelength of 308 nm and emission wavelength of 412 nm (Oakley, 1978). Urinary total salicylic acid concentrations were measured photometrically (Levy & Procknal, 1968).

No interference of one drug by another was demonstrated in either plasma or urine assays.

Statistical analysis

All results are expressed as mean ± s.d. unless otherwise stated. One way analysis of variance was used to assess inter- and intra-subject variability and analysis of covariance (regression approach) was used to study the relationships between gastric emptying and oro-caecal transit and drug kinetics, by subject. Paired *t*-tests, using the mean of the three basal studies, were used to assess the effects of treatment with agents affecting transit times. Area under the plasma drug concentration-time curve (AUC) was calculated from 0 to 24 h, using the linear trapezoidal rule.

Results

Baseline variability in transit and drug kinetics

The results of gastric emptying and oro-caecal transit measurements during the three baseline studies are shown in Table 1. The mean gastric half-emptying time was 33 ± 19 min. The time to 20% emptying was 14 ± 12 min and time to 80% emptying was 68 ± 30 min. Breath hydrogen levels began to rise 64 ± 34 min after ingestion of the test solution and peak levels occurred at 123 ± 51 min.

Analysis of covariance revealed highly significant correlations between all phases of gastric emptying, by subject (t_{20} vs t_{50} , $F = 110$, $P < 0.001$; t_{50} vs t_{80} , $F = 36.8$, $P < 0.001$; t_{20} vs t_{80} , $F = 14.4$, $P = 0.003$). There were no significant relationships, however, between measures of gastric emptying and oro-caecal transit. Furthermore, time to first breath hydrogen rise and peak hydrogen response were not significantly correlated ($F = 1.59$, $P = 0.23$).

Gastrointestinal transit varied little when the same subject was studied on three separate occasions but between subject differences were considerable. For gastric emptying, inter-subject variability was 4 to 10 times greater and for oro-caecal transit 15 to 28 times greater than intra-subject variability.

Table 2 shows the maximum plasma drug concentration, time of maximum plasma drug concentration, total area under the plasma drug concentration-time curve and 24 h urinary excretion of the four drugs during the three baseline studies. Variability in each of the parameters was marked and for atenolol and frusemide, in particular, largely due to between subject differences.

Analysis of covariance revealed a highly significant positive correlation between the time of maximum plasma salicylic acid concentration (t_{max}) and gastric emptying by subject. This relationship held for all phases of gastric emptying (t_{20} $F = 84.2$, $P < 0.01$; t_{50} $F = 52.6$, $P < 0.001$; t_{80} $F = 25.4$, $P < 0.01$) and is shown, for gastric half-emptying time (t_{50}) in Figure 1. All other kinetic parameters, however, were unrelated to measures of either gastric emptying or oro-caecal transit.

Effects of metoclopramide and codeine phosphate on transit and drug kinetics

The individual effects of oral metoclopramide and codeine phosphate pretreatment on gastric emptying and oro-caecal transit are shown in Figures 2 and 3. Metoclopramide had no significant effect on any measure of gastric emptying. The time to first rise in breath hydrogen level (OCR) and the time to peak hydrogen response (OCP) were both decreased following metoclopramide but these differences were not significant (OCR: metoclopramide 48 ± 20 vs baseline 64 ± 34 min, $P = 0.13$; OCP: metoclopramide 101 ± 29 vs baseline 123 ± 51 min, $P = 0.09$). Codeine phosphate pretreatment also left gastric emptying unchanged but

Table 1 Baseline variability in gastric emptying and oro-caecal transit

	Mean (Range)	Coefficient of variation (%)	Inter- to intra- subject mean square ratio (P value)
<i>Gastric emptying (min)</i>			
t_{20}	14 (2–14)	86	4.1 (0.02)
t_{50}	33 (11–76)	56	4.9 (0.01)
t_{80}	68 (27–120)	45	10.8 (0.0004)
<i>Oro-caecal transit (min)</i>			
OCR	64 (25–150)	53	15.0 (0.0001)
OCP	123 (60–230)	41	28.9 (<0.0001)

t_{20} , t_{50} , t_{80} Time to 20%, 50% and 80% gastric emptying.

OCR Time to first rise in breath hydrogen level (oro-caecal transit of the head of solution).

OCP Time to peak rise in breath hydrogen level (oro-caecal transit complete).

Table 2 Baseline variability in drug kinetics

	Mean (Range)	Coefficient of variation (%)	Inter- to intra- subject mean square ratio (P value)
<i>Frusemide</i>			
$C_{\max}$ (ng ml ⁻¹)	322 (178–475)	30	19.8 (<0.0001)
$t_{\max}$ (min)	60.8 (45–90)	25	3.70 (0.03)
AUC (mg l ⁻¹ h)	0.632 (0.203–0.985)	35	12.5 (0.0002)
24 h urine excretion (mg)	3.97 (2.18–6.46)	30	4.0 (0.22)
<i>Atenolol</i>			
$C_{\max}$ (ng ml ⁻¹)	42.1 (19.1–56.0)	24	9.8 (0.0006)
$t_{\max}$ (min)	158 (90–180)	20	3.0 (0.05)
AUC (mg l ⁻¹ h)	0.490 (0.282–0.755)	32	16.4 (0.0001)
24 h urine excretion (mg)	3.09 (2.09–3.79)	16	6.7 (0.003)
<i>Hydrochlorothiazide</i>			
$C_{\max}$ (ng ml ⁻¹)	84.3 (48.6–146)	28	0.74 (0.61)
$t_{\max}$ (min)	180 (90–300)	37	3.05 (0.06)
AUC (mg l ⁻¹ h)	0.448 (0.260–0.697)	28	3.47 (0.04)
24 h urine excretion (mg)	3.03 (1.96–4.65)	22	1.56 (0.24)
<i>Salicylic acid</i>			
$C_{\max}$ (ng ml ⁻¹)	45.7 (34.2–56.5)	13	7.11 (<0.002)
$t_{\max}$ (min)	51.1 (20–120)	51	3.42 (0.04)
AUC (mg l ⁻¹ h)	255 (188–358)	18	4.26 (0.02)
24 h urine excretion (mg)	408 (282–516)	19	0.45 (0.80)

Figure 1 The relationship between gastric half-emptying time (t_{50}) and time to maximum salicylic acid concentration ($t_{\max}$) during three baseline studies ($n = 6$, analysis of covariance $F = 52.6$, $P < 0.001$). Each symbol represents results from a single individual.

brought about an almost two-fold prolongation in oro-caecal transit time. The time to first rise in breath hydrogen level increased from 64 ± 34 min to 127 ± 37 min, $P < 0.01$ and the time to peak breath hydrogen response increased from 123 ± 51 min to 215 ± 59 min, $P < 0.002$.

Figure 2 Effects of treatment of metoclopramide (M) and codeine phosphate (C) on gastric emptying. t_{20} = time to 20% emptying, t_{50} = time to 50% emptying, t_{80} = time to 80% emptying. B = mean of baseline studies ($n = 3$). No significant differences.

The individual effects of metoclopramide and codeine pretreatment on the 24 h urinary excretion of the four study drugs are shown in Figure 4. Neither metoclopramide nor codeine had a significant effect on urinary drug excretion. $C_{\max}$, $t_{\max}$ and AUC were similarly unaffected (Table 3).

Discussion

In an attempt to explain variability in drug absorption we have studied the relationships between gastrointestinal transit and the absorption of frusemide,

Figure 3 Effects of treatment with drugs affecting motility on oro-caecal transit. OCR = time to first rise in breath hydrogen levels, OCP = time to peak breath hydrogen response, M = metoclopramide treatment, B = mean of baseline studies ($n = 3$), C = codeine treatment. OCR: codeine vs baseline $P < 0.01$; OCP: codeine vs baseline $P < 0.002$.

atenolol, hydrochlorothiazide and salicylic acid. The drugs are all in common clinical use and are frequently prescribed in combination. The absorption of atenolol, hydrochlorothiazide and frusemide is relatively slow and incomplete whereas the absorption of salicylic acid is rapid and complete (Beerman & Groschinsky-Grind, 1977; Mason *et al.*, 1979; Needs & Brooks, 1985; Waller *et al.*, 1985). There is no evidence of drug interactions within the group (Miners, 1989; Nakahama *et al.*, 1988; Sabanathan *et al.*, 1987) and all, with the exception of salicylic acid, are excreted largely unchanged in the urine so that cumulative urinary excretion may be used as an index of the extent of absorption. Although salicylic acid is extensively metabolised, total urinary salicylate is a quantitative measure of the amount of salicylic acid absorbed. In the present study we used a multicomponent

aqueous solution to obviate the problems of dissolution and to permit comparisons between drugs.

The gastrointestinal transit of our multicomponent solution was similar to that reported by others, using comparable test solutions and conditions (Brunetto *et al.*, 1990). The gastric half-emptying time of the solution was approximately 30 min and oro-caecal transit of the head of the solution was approximately 60 min. It is important to remember, however, that oro-caecal transit is a composite measure of gastric and small bowel transit. Despite this relationship we could find no correlation between measures of gastric emptying and oro-caecal transit. This supports previous findings suggesting that gastric emptying and small bowel transit are independent variables (Cobden *et al.*, 1983; Davis *et al.*, 1986; Read *et al.*, 1982).

Although each subject followed a strictly standardised protocol, baseline variability in gastric emptying and oro-caecal transit time was marked. This variability was mostly accounted for by considerable between subject differences, transit varied little when the same subject was studied repeatedly. Such inter-subject variability has been noted by others (La Brooy *et al.*, 1983; Staniforth, 1987) and raises the possibility that variability in transit may explain variability in drug absorption.

Salicylic acid is rapidly and completely absorbed from the gut (Rowland *et al.*, 1972). It was not surprising then, that changes in oro-caecal transit did not correlate with extent of absorption. Salicylic acid was included in the test solution to study the influence of gastric emptying on the rate of absorption and to act as a measure of compliance. The strong correlation between all phases of gastric emptying and the time to maximum plasma salicylic acid concentration (C_{max}) suggests that absorption is rate-limited by gastric emptying. Other rapidly absorbed drugs have a similar relationship to gastric emptying (Clements *et al.*, 1978). There were no significant correlations between gastric emptying and the rate of absorption of frusemide, atenolol and hydrochlorothiazide suggesting less rapid absorption.

Frusemide, atenolol and hydrochlorothiazide are all incompletely absorbed from the gastrointestinal tract. We therefore expected to find positive correlations between the extent of absorption of these drugs and oro-caecal transit, but none were present. As this may have been related to the relatively modest intra-subject

Figure 4 Effects of treatment with metoclopramide (M) and codeine phosphate (C) on 24 h urinary drug excretion. B = mean of baseline studies ($n = 3$). No significant differences.

Table 3 Effects of metoclopramide and codeine pretreatment on drug kinetics

	Metoclopramide	Baseline	Codeine
<i>Frusemide</i>			
$C_{\max}$ (ng ml ⁻¹)	379 ± 51.0	322 ± 39.8	374 ± 139
$t_{\max}$ (min)	60.0 ± 6.7	60.8 ± 5.1	65.0 ± 8.4
AUC (mg l ⁻¹ h)	0.743 ± 0.106	0.632 ± 0.088	0.747 ± 0.210
24 h urine excretion (mg)	6.01 ± 1.52	3.97 ± 0.41	4.06 ± 0.77
<i>Atenolol</i>			
$C_{\max}$ (ng ml ⁻¹)	44.2 ± 5.88	42.1 ± 3.99	40.0 ± 3.74
$t_{\max}$ (min)	150 ± 30.0	158 ± 10.5	190 ± 24.1
AUC (mg l ⁻¹ h)	0.480 ± 0.069	0.490 ± 0.063	0.500 ± 0.060
24 h urine excretion (mg)	2.95 ± 0.27	3.09 ± 0.19	3.01 ± 0.28
<i>Hydrochlorothiazide</i>			
$C_{\max}$ (ng ml ⁻¹)	83.6 ± 9.8	84.9 ± 5.1	82.6 ± 10.1
$t_{\max}$ (min)	144 ± 14.7	185 ± 23.3	168 ± 12.0
AUC (mg l ⁻¹ h)	0.423 ± 0.075	0.455 ± 0.043	0.423 ± 0.057
24 h urine excretion (mg)	3.66 ± 0.71	3.03 ± 0.18	3.04 ± 0.22
<i>Salicylic acid</i>			
$C_{\max}$ (ng ml ⁻¹)	42.1 ± 2.5	45.7 ± 2.3	46.0 ± 1.3
$t_{\max}$ (min)	63.3 ± 14.7	51.1 ± 8.6	65.8 ± 14.3
AUC (mg l ⁻¹ h)	242 ± 19.7	257 ± 16.4	258 ± 22.7
24 h urine excretion (mg)	427 ± 35.9	408 ± 13.4	420 ± 18.6

variability in transit under basal conditions, pharmacological manipulation of transit with metoclopramide and codeine was thought to be a useful means of exploring this relationship further.

Previous studies have shown that metoclopramide accelerates oro-caecal transit and the gastric emptying of solids but has little effect on the emptying of liquids (Ramsbottom & Hunt, 1970; Rumessen *et al.*, 1989; Staniforth, 1987). Codeine appears to have little effect on gastric emptying (Bajorek *et al.*, 1978) but oro-caecal transit is consistently delayed (O'Brien *et al.*, 1988). Intestinal perfusion studies suggest that codeine acts principally by slowing jejunal transit (Schiller *et al.*, 1982).

In the present study metoclopramide had no effect on the gastric emptying of the test solution and although oro-caecal transit times were reduced the differences were not statistically significant. We were therefore unable to study the effects of pharmacological acceleration of transit on drug absorption. It is not clear why metoclopramide failed to speed transit but it may be that the rather rapid transit times seen under baseline conditions limited significant acceleration. It is worth noting that subjects with the slowest baseline transit times responded most to metoclopramide.

Codeine pretreatment also failed to influence gastric emptying but caused a two-fold delay in oro-caecal transit. Despite this delay, the extent of absorption of frusemide, atenolol and hydrochlorothiazide was not increased. This suggests that within the limits of this experiment oro-caecal transit time is not an important determinant of absorption and that differences in transit are unlikely to account for the observed variability in absorption.

Previous attempts to enhance intestinal absorption by slowing transit with opiates or anticholinergic agents

have met with varied success. In patients with high output ileostomies and in those with post-vagotomy diarrhoea opiates improves water, electrolyte and glucose malabsorption (Newton, 1978; O'Brien *et al.*, 1988). Furthermore, the extent of absorption of small molecules such as xylose and mannitol may be increased in healthy volunteers (Brunetto *et al.*, 1990; Fordtran *et al.*, 1962). The absorption of larger molecules, however, such as drugs, seems more resistant to manipulation. Pretreatment with anticholinergic agents does not enhance the absorption of other incompletely absorbed drugs such as cimetidine and lactulose (Brunetto *et al.*, 1990; Kanto *et al.*, 1981). Some have reported enhanced drug absorption with anticholinergic agents but this is probably related to improved tablet dissolution due to the associated delay in gastric emptying (Beerman *et al.*, 1978; Jaffe, 1975; Manninen *et al.*, 1973; Regardh *et al.*, 1981).

The reason why changes in small bowel transit failed to influence drug absorption is not clear. It may be that the experimental techniques employed are insensitive measures of contact time with the small intestinal mucosa. Furthermore, if segmental transit is important effects may have been missed by measurement of total mouth to caecum transit time. It seems more likely, however, that the effects of slowing bulk phase transit through the small intestine have been offset by other factors, such as poorer luminal mixing. Whatever the reason, it appears that factors other than small bowel transit account for the observed inter- and intra-subject variability in frusemide, atenolol and hydrochlorothiazide absorption.

Finally, we were surprised to find that the extent of absorption of atenolol and hydrochlorothiazide was considerably lower in the present study than in previous published reports. Rates of absorption, as judged by the time to maximum plasma concentrations all appeared

normal and both the rate and extent of frusemide and salicylic acid absorption were similar to reported values. In a companion study we show that the incorporation of lactulose into the test solution is responsible, and that this effect appears independent of changes in transit time.

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