Influence of Polyethylene Glycol 400 on the Gastrointestinal Absorption of Ranitidine

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Purpose. To investigate the effect of co-administered polyethylene glycol 400 (PEG 400), a pharmaceutical excipient previously shown to accelerate small intestinal transit, on the absorption characteristics of ranitidine from the gastrointestinal tract.

Methods. Ten healthy male volunteers each received, on two separate occasions, an immediate-release pellet formulation of ranitidine (150 mg) encapsulated within a hard gelatin capsule and a liquid preparation consisting of 150 ml orange juice (control) or 150 ml orange juice containing 10 g PEG 400 (test). The liquid preparations were also radiolabelled with indium-111 to allow their transit through the gastrointestinal tract to be followed using a gamma camera. On a further occasion an intravenous injection of ranitidine (50 mg) was administered. Blood samples were taken over a 12 h period on each study day to allow a ranitidine plasma and subsequent absorption rate profile to be generated for each oral formulation. Urine was collected for 24 h and assessed for PEG 400 concentration.

Results. The absolute bioavailability of ranitidine from the pellet formulation was significantly reduced by 31% (from 51% to 35%) and small intestinal liquid transit time was significantly shortened by 37% (from 226 min to 143 min) as a consequence of PEG 400 in the test preparation. PEG 400 also affected the rate of ranitidine absorption, with major differences noted in the mean absorption time and C_{max} parameters. The appearance of double peaks were less evident in the ranitidine pharmacokinetic profiles in the presence of PEG 400, and little or no correlation was observed between the absorption of ranitidine and PEG 400.

Conclusions. These results clearly demonstrate that PEG 400 adversely influences the gastrointestinal absorption of ranitidine. This in turn has ramifications for the use of PEG 400 as a pharmaceutical excipient in oral formulations.

KEY WORDS: polyethylene glycol 400; poorly water-soluble drugs; gastrointestinal transit; permeability; bioavailability; gamma scintigraphy; ranitidine; double peaks.

INTRODUCTION

The polyethylene glycols (PEGs) are a class of polymer that are widely used in a variety of pharmaceutical formulations including parenteral, topical, ophthalmic, oral and rectal preparations (1). These polymers, essentially polymers of oxyethylene glycol, exist in a variety of molecular weight grades, ranging from 200 to 35,000. The low molecular weight PEGs (<600) are liquid in nature and are routinely employed as vehicles for poorly water-soluble drugs (2).

Poorly water-soluble drugs usually present oral bioavailability problems as a result of limited dissolution within the gut. The use of PEGs should enhance the solubility of such drugs and in theory increase oral bioavailability. In some instances, however, this approach has given rise to unexpected results. For example, the bioavailability of griseofulvin, a poorly water-soluble drug, in rabbits was markedly lower from a solution formulation containing 10 g of PEG 400 than from a conventional powder formulation in a hard gelatin capsule (3). This finding was in spite of the solubility of the drug being considerably enhanced in the presence of PEG 400, and is contrary to the commonly held assumption that solution formulations should be no less, if not more, bioavailable than solid dosage forms. The authors hypothesized that differential rates of transit of the two formulations through the gut rather than precipitation of the drug from the solution formulation was responsible for this untoward effect. In a recent scintigraphic study in humans (4), we have shown that 10 g of PEG 400 has a significant accelerating effect on small intestinal transit, resulting in a 35% reduction in liquid transit time, thereby providing support for the previously proposed hypothesis. For drugs that are largely absorbed from the small intestine, the primary site of absorption, it would follow that any reduction in the residence time of the drug within this region of the gut may lead to a detrimental effect on oral absorption.

The primary aim of this study was to assess whether PEG 400 has an adverse influence on the absorption of ranitidine, a drug known to be primarily absorbed from the small intestine (5). The study was further concerned with exploring the double peak phenomenon associated with the plasma profiles of ranitidine. Moreover, as both ranitidine and PEG 400 are considered to be absorbed across the gastrointestinal mucosa via the paracellular route (6,7), it would be of interest to note whether there is a relationship between the absorption of these two compounds.

MATERIALS AND METHODS

Dosage Forms

The liquid preparation consisted of 150 ml orange juice (Tesco Stores Ltd., Cheshunt, UK). Each aliquot of orange juice contained either 0 or 10 g of PEG 400 (Sigma-Aldrich Company, Poole, UK). Each liquid preparation was radiolabelled with indium-111 (^{111}In) to an activity of 2.5 MBq using ^{111}In-diethylenetriaminepentaacetic acid (^{111}In-DTPA) solution. The osmolality of the two liquid preparations was measured using an osmometer (model 200, Camlab, Cambridge, UK). The osmolality of the orange juice and PEG 400-containing orange juice were 606 mOsm kg^{-1} and 951 mOsm kg^{-1}, respectively.

The model drug ranitidine (GlaxoSmithKline, Ware, UK) was formulated into pellets by the process of extrusion-spheronisation (8). A pellet formulation loaded with 50% ranitidine, in the form of the hydrochloride salt, was found to

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display the characteristics of an immediate-release formulation (>90% drug release within 15 min of dissolution testing in 0.1N hydrochloric acid). Prior to administration, the pellets, of size 1.4–1.7 mm, were filled into size 0 hard gelatin capsules (Capsugel, Colmar, France) to a nominal fill weight of 340 mg (≡168 mg ranitidine hydrochloride ≡150 mg ranitidine).

Ranitidine was also obtained in the form of an intravenous preparation (Zantac, 50 mg/2ml) from GlaxoSmithKline, Ware, UK.

Study Protocol

Ten healthy male volunteers participated in an open three-way crossover study after providing written informed consent. All were non-smokers, were not taking any medication and had no history of gastrointestinal disease. The experimental protocol was approved by the Joint UCL/UCLH Committees on the Ethics of Human Research. Authority to administer radiopharmaceuticals was obtained from the Administration of Radioactive Substances Advisory Committee (ARSAC) at the Department of Health. The study was conducted in accordance with the provisions of the declaration of Helsinki (1964) and its subsequent revisions. Each volunteer reported to the study center on the morning of the study, after adherence to an overnight fast. A small in-dwelling cannula was positioned in a forearm vein for the easy withdrawal of blood samples, and kept patent with regular heparin flushes throughout the course of the study. In the case of the oral administrations, each volunteer received on two separate occasions the following treatments in a randomized order: 150 ml of orange juice containing 0 (control) or 10 g of PEG 400 (test). Each volunteer also concurrently received a capsule containing the ranitidine pellets. A small sealed point source of 0.1 MBq ^{111}In was taped to the abdominal skin at the most lateral position of the right lower costal margin to act as an anatomical reference marker. Imaging was performed using a double-headed gamma camera (Maxxus, General Electric Medical Systems, Milwaukee, WI, USA) fitted with two opposed detectors, each having a 508 × 368 mm useful field of view and capable of simultaneous data acquisition. Each detector was fitted with a medium energy parallel hole collimator suitable for ^{111}In imaging. After administration of the preparations, the volunteer was positioned supine between the two detectors of the gamma camera. Simultaneous anterior and posterior images of 30 s duration were initially acquired every 5 min and then at 10 to 15 min intervals after the liquid had emptied from the stomach. In between image acquisitions, the volunteer was free to move away from the camera. A standard lunch was provided 4 h post dose, and water and other non-alcoholic drinks were available *ad libitum* from this point onwards. Images were digitally recorded using an integrated computer system (Starcam 3200i, General Electric Medical Systems, Milwaukee, WI, USA) and archived onto optical disk for subsequent analysis. In addition to imaging, blood samples were also collected throughout the course of the study. Blood samples of volume 6 ml were collected at 0 (pre-dose), 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, and 12 h. These were centrifuged at 3000 rpm for 10 min, and the resultant upper plasma layer was transferred to separate plastic containers and kept frozen at –20°C prior to analysis. Urine collections were also made during the PEG 400 (test) arm of the study, comprising the collection and measurement of bladder output over the following time periods: 0 to 2, 2 to 4, 4 to 6, 6 to 12, and 12 to 24 h, and the retention and storage of a 20 ml aliquot at –20°C.

On the third study day, the intravenous preparation (Zantac) was diluted to 20 ml with normal saline and administered over a period of 2 min into a forearm vein. Blood samples (0 (pre-dose), 0.05, 0.08, 0.17, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, and 12 h) were collected through a cannula positioned in a forearm vein in the opposite arm.

Plasma and Urine Analysis

The plasma samples were assayed in duplicate for ranitidine content using a validated high performance liquid chromatography (HPLC) method (9).

The urine samples were assayed in duplicate for PEG 400 content using a validated reversed phase HPLC method with refractive index detection as previously described by Young *et al.* (10). The assay was able to separate nine peaks (PEG 400 is composed of at least nine molecular weight fractions ranging from 238 to 590), although three of these were difficult to accurately quantify. The six main peaks, corresponding to molecular weight fractions 326, 370, 414, 458, 502, and 546, were therefore quantified. The combined areas of these six peaks were used as a measure of total PEG 400 excretion.

Pharmacokinetic Analysis

Plasma ranitidine concentration time profiles were constructed for both oral treatments in each volunteer. C_{max} and t_{max} were read directly from the curves. For a more thorough analysis of ranitidine absorption, the data were analyzed using the deconvolution technique of maximum entropy (11–13), with the intravenous data acting as the weighting function (MADAME software package, version 2.01, Maximum Entropy Data Consultants Ltd., Cambridge, UK). The program generated absorption rate profiles as well as absolute bioavailability and mean absorption time data for each of the preparations in the individual volunteers.

PEG 400 excretion was quantified by measuring the concentration of polymer present in the different timed urine samples, correcting for urine volume to obtain exact quantities, and then pooling the results together to obtain the total amount excreted in 24 h.

Scintigraphic Data Analysis

Processing of image data was performed using a Hermes image processing workstation (Nuclear Diagnostics, Stockholm, Sweden). The series of ^{111}In liquid images acquired for each volunteer was replayed on the computer system. Three regions of interest were highlighted on the computer screen by cursor, representing the stomach, cecum/colon and anatomical marker. The full sequence of images was viewed to check for movement of the volunteer by referring to the anatomical marker. Any volunteer movement was then corrected using a proprietary motion correction package (Nuclear Diagnostics, Stockholm, Sweden). The counts recorded for each region of interest by each detector were calculated by the computer for each image. These values were corrected for background count rates by subtracting from each pixel in the region of interest, the mean counts per pixel from a region at the edge of each image. The geometric mean of the anterior

and posterior counts was calculated to correct for differential attenuation of the radiation with varying depth of source (14). These counts were then corrected for physical decay of the radionuclide. Finally, the corrected geometric mean counts for the regions of interest were expressed as percentages of the total counts recorded initially when all the administered activity was in the stomach region. The time course of gastric emptying and cecum/colon arrival could then be estimated from the plot of percentage activity in these regions vs. time.

The gastrointestinal transit data were quantitatively assessed using statistical moments to calculate the mean gastric residence time (MGRT) and mean cecum arrival time (MCAT) (15). The difference between the MGRT and MCAT represents the mean small intestinal transit time (MSITT).

Statistical Analysis

Statistical analysis by way of a paired Student's *t* test was performed on the pharmacokinetic and scintigraphic data to assess the impact of PEG 400 on ranitidine absorption and gastrointestinal transit.

RESULTS AND DISCUSSION

The ranitidine plasma and absorption rate profiles, in the absence (control) and presence (test) of PEG 400, for one representative subject (volunteer 10) are shown in Fig. 1. The overall mean profiles are depicted in Fig. 2. The ranitidine and PEG 400 pharmacokinetic parameters are presented for each individual in Table I. The mean absolute bioavailability of the control formulation was 51% (range 40–83%), which is in close agreement to literature values (17). In the presence of PEG 400, however, the bioavailability of ranitidine from the pellet formulation was significantly reduced by 31% to 35% (range 28–52%) ($p < 0.001$). Similarly, the mean absorption time, C_{max} and t_{max} values were all lower, but not significantly so for the t_{max} data, in the presence of PEG 400.

The gastrointestinal liquid transit data, in the absence (control) and presence (test) of PEG 400, for each individual are presented in Table II. Gastric emptying was rapid for both liquid preparations, although slightly longer for the PEG 400-containing preparation (mean MGRT of 24 min vs. 17 min for the control, $p = 0.116$). The reason for this slight delay may be attributed to the higher osmolality of the PEG 400-containing liquid preparation (951 mOsm kg^{-1} as compared to 606 mOsm kg^{-1} for the control). The cecum arrival times of the two preparations were significantly different (mean MCAT of 243 min for the control vs. mean MCAT of 167 min for the test preparation, $p < 0.001$). As the gastric emptying times of the two preparations were very similar, differential rates of transit through the small intestine were responsible for the dissimilar cecum arrival times. The mean MSITT for the control preparation was 226 min. The corresponding value for the PEG 400-containing preparation was significantly shorter at 143 min ($p < 0.001$). This 37% reduction in transit time clearly demonstrates that PEG 400 has a marked accelerating effect on small intestinal transit. This finding is consistent with our previous study, which showed that the presence of PEG 400 led to a 35% reduction in liquid transit time through the small intestine (4). The mechanism behind this transit effect is probably related to PEG 400 being incompletely absorbed from the gut (16). Soon after administration, the hypertonic PEG 400-containing liquid preparation will empty from the stomach and be rapidly made isotonic by the secretion of fluid from the systemic circulation into the lumen of the intestine. Furthermore, the osmotic activity of unabsorbed PEG 400 within the intestine will be offset by the retention of fluid in the lumen. This net secretion and inhibition of absorption of fluid will therefore lead to an increase in gastrointestinal fluid volume, which in turn will stimulate peristalsis and hence quicken transit through the small intestine.

Since ranitidine is primarily absorbed from the small intestine (5), the untoward effect of PEG 400 on the rate and extent of ranitidine absorption observed in this study would appear to be linked to the accelerating effect of the polymer on small intestinal transit, which reduces the contact time of the drug with this region of the gastrointestinal tract. Although ranitidine was administered in the form of a solid pellet formulation rather than in solution, the rapid *in vitro* dissolution of the formulation suggests that it would dissolve rapidly in the stomach and be transported through the intestine with the liquid preparation, and therefore the liquid transit data should provide a reasonable indicator of the position of the drug in the gut. Koch *et al.* (18) have shown that sodium acid pyrophosphate, a pharmaceutical excipient utilized in effervescent formulations, reduces both small intestinal transit time and ranitidine bioavailability. Likewise, Adkin *et al.* (19) found that another effervescent excipient mannitol not only hastens small intestinal transit but also reduces the extent of absorption of cimetidine, a drug from the same pharmacological class as ranitidine.

On comparing each individual's pharmacokinetic and transit data, it is apparent that those who display a large reduction in bioavailability as a result of PEG 400 do not necessarily show a correspondingly large reduction in small intestinal transit time (e.g. volunteer 2), thereby suggesting that transit effects may not be the sole reason for the changes in ranitidine absorption. An additional possibility may be that PEG 400 has a direct effect on the gastrointestinal epithelium, which influences the permeation of ranitidine. However, a recent study using Caco-2 cells has shown that PEG 400 has no effect on the transport of ranitidine (20). A further possible factor may be related to the poorly absorbable and osmotically active nature of PEG 400, which after administration will draw fluid from the systemic circulation into the lumen of the gut. As ranitidine is believed to permeate across the gastrointestinal mucosa via the paracellular route (6), a route of absorption that is largely dependent on water absorption, this influx of fluid may hinder the absorption of the drug. Moreover, the increased fluid load within the lumen of the intestine will decrease not only the concentration of the drug present in solution but also the concentration gradient across the mucosa, which may further retard ranitidine absorption. Along similar lines, a previous study in humans has shown that the absorption of a series of model compounds was negatively influenced by the presence of a non-absorbable osmotic load in the gut (21). Therefore, in addition to accelerated small intestinal transit, trans-mucosal fluid fluxes may also play a role in the reduced bioavailability of ranitidine in the presence of PEG 400.

Inspection of the ranitidine pharmacokinetic profiles in the absence of PEG 400 (control) (Figs. 1 and 2.) clearly

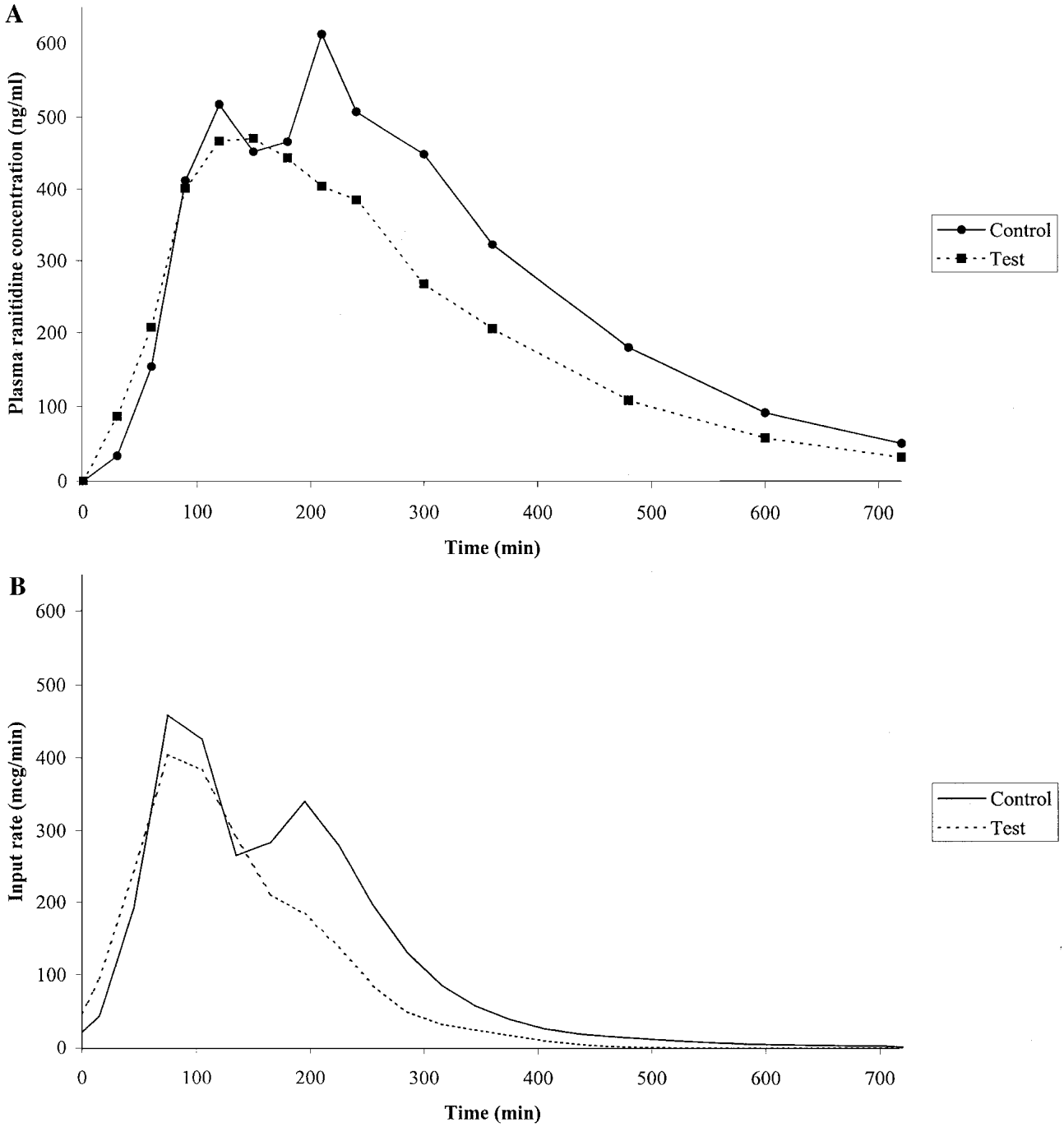

Fig. 1. (A) Ranitidine plasma profiles for a representative subject (volunteer 10) in the absence (control) and presence (test) of PEG 400, (B) Ranitidine absorption rate profiles for a representative subject (volunteer 10) in the absence (control) and presence (test) of PEG 400 (For ease of clarity, individual data point markers have been omitted as absorption rates were calculated at 5 min intervals)

reveals the presence of two distinct maxima. In fact, double peaks were evident, to varying degrees, in the individual plasma profiles of all ten volunteers. This observation has been noted by other workers (22,23), and is not unique to ranitidine, having been observed with other H_2-receptor antagonists including cimetidine (24) and famotidine (25). This phenomenon was less pronounced in the presence of PEG 400, with only a single peak present in six out of the ten volunteer plasma profiles. Moreover, double peaks were not detected in any of the individual plasma ranitidine-time curves following intravenous administration. A number of hypotheses have been proposed to explain the appearance of double peaks following oral administration, including delayed gastric emptying of a portion of the administered dose (26), enterohepatic recycling or secretion of the drug into the lumen of the gut (17), sequestration of a portion of the drug in the hepatic parenchymal tissue with subsequent bolus release into the systemic circulation (5), and discontinuous absorption from the gut (27). In the present study, the first peak appeared in the plasma and absorption rate profiles of the

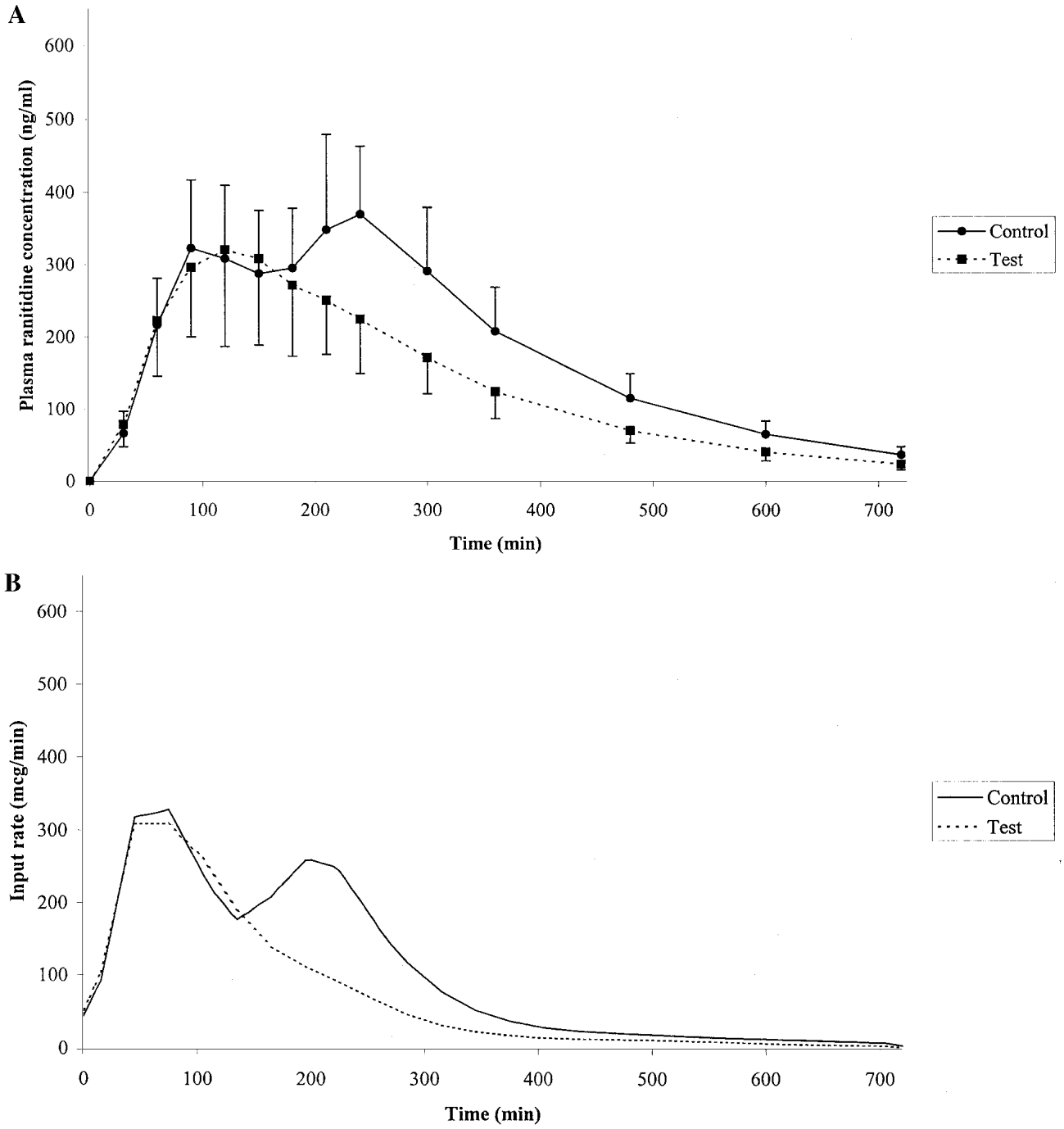

Fig. 2. (A) Mean (± s.d.) ranitidine plasma profiles in the absence (control) and presence (test) of PEG 400. (B) Mean ranitidine absorption rate profiles in the absence (control) and presence (test) of PEG 400 (for ease of clarity, individual data point markers and error bars have been omitted as absorption rates were calculated at 5 min intervals)

control treatment between 1 to 1.5 h and the second peak appeared 3 to 4 h after oral administration. Based on the transit data, which indicated a small intestinal transit time of the order of 4 h, the first peak could imply absorption from the proximal small intestine, whereas the second peak could represent absorption from a more distal site in the small intestine rather than the colon, as absorption from this region is very limited (5). In line with this, Gramatte *et al.* (28) have previously shown by infusing ranitidine solution into different regions of the human small intestine that absorption was highest from the proximal duodenal-jejunum and distal jejunum-ileum regions, with no absorption from the mid jejunum region. In a more recent study in humans, Pithavala *et al.* (29) found that the rate and extent of ranitidine absorption was virtually identical from the jejunum and ileum. In the presence of PEG 400, the double peaks in the ranitidine profiles were less frequent, and more often only a single, relatively broad peak was observed at around 1.5 to 2 h. In terms of an explanation for this, accelerated transit through the small intestine would effectively reduce the "distance" between the two ranitidine absorption sites in the small intestine. This would not only limit the time available for ranitidine absorp-

Table I. Ranitidine Pharmacokinetic Data in the Absence (Control) and Presence (test) of PEG 400, and PEG 400 Excretion Data

	Bioavailability (%)		Mean absorption time (min)		C_{max} (ng/ml)		t_{max} (min)		PEG 400
Volunteer	Control	Test	Control	Test	Control	Test	Control	Test	excretion (%)
1	40	32	144	126	319	253	240	180	25
2	53	32	191	184	338	209	300	240	35
3	47	32	178	169	338	265	90	120	16
4	50	36	171	128	449	473	90	120	28
5	44	36	160	148	397	278	90	120	20
6	48	33	204	116	528	496	240	120	28
7	47	30	204	174	314	205	120	90	25
8	36	28	210	147	323	378	90	150	34
9	83	52	201	145	461	398	240	120	34
10	59	43	174	135	612	471	210	150	33
Mean	51	35	184	147	408	343	171	141	28
s.d.	13	7	22	22	102	114	83	43	6
P value	<0.001		0.002		0.011		0.177		

tion, as evidenced by the shorter mean absorption times, but also result in the appearance of two absorption peaks that are closer together in the pharmacokinetic profiles. Such a trend was observed in four out of the ten volunteer plasma profiles. Moreover, further convergence of the two absorption peaks, possibly as a result of even faster small intestinal transit, would lead to the appearance of a single peak, as shown in the pharmacokinetic profiles of volunteer 10 (Fig. 1). This trend was mirrored in a further five individual plasma profiles, and can also be seen in the overall mean profiles (Fig. 2). Extrapolating these results to the normal situation in the absence of PEG 400, the reason for the appearance of two peaks in the plasma profiles after oral administration of ranitidine would therefore appear to be related to the intestinal residence time (19,30) and possibly regional absorption differences within the small intestine (28).

In addition to absorbing nutrients, electrolytes and water, the gastrointestinal epithelium also provides a barrier to the absorption of larger, potentially harmful compounds. A number of clinical studies have demonstrated a defect in intestinal barrier function in patients with Crohn's disease, ulcerative colitis, celiac disease, and rheumatoid arthritis among others (7,31–33). These defects were detected using a wide variety of non-invasive permeability probes including ^{51}Cr-ethylenediaminetetraacetic acid (^{51}Cr-EDTA), lactulose, rhamnose, mannitol and PEG 400 (7,31–33). Of these, PEG 400, being a mixture of molecular weight fractions and a polymer that is not metabolized and hence excreted unchanged in the urine, has been deemed to exhibit the ideal characteristics of a permeability probe (16,34). Since both PEG 400 (7,16) and ranitidine (5,6) are hydrophilic molecules that are believed to be absorbed, mainly from the small intestine, by the paracellular route, it would be noteworthy to assess whether there is a relationship between the absorption of these two compounds and elucidate whether PEG 400 is a suitable absorption marker for drugs absorbed by this route. On average, 28% (range 16–35%) of the orally administered 10 g dose of PEG 400 was recovered in the urine, which is within the range reported in the literature (16,32). The remainder of the dose is likely to have passed through the gut intact and subsequently been eliminated in the feces (16). More than 75% of the dose collected in the urine was excreted within the first 4 h after administration, thereby implying that absorption predominantly occurred from the small intestine. A comparison of each individual's PEG 400 excretion data against their corresponding ra-

Table II. Gastrointestinal Liquid Transit Data in the Absence (Control) and Presence (Test) of PEG 400

	Mean gastric residence time (MGRT) (min)		Mean small intestinal transit time (MSITT) (min)		Mean cecum arrival time (MCAT) (min)	
Volunteer	Control	Test	Control	Test	Control	Test
1	13	26	235	136	248	162
2	11	26	238	209	249	235
3	29	9	223	150	252	159
4	16	27	291	144	307	171
5	15	38	216	125	231	163
6	21	37	185	99	206	136
7	11	13	213	156	224	169
8	26	14	288	160	314	174
9	13	23	199	149	212	172
10	10	27	174	106	184	133
Mean	17	24	226	143	243	167
s.d.	7	10	39	31	42	28
P value	0.116		<0.001		<0.001	

nitidine bioavailability data can be seen in Table I. Considerable variability can be observed in these results and the apparent lack of any correlation between these parameters would suggest that there is no meaningful relationship between the absorption of PEG 400 and ranitidine *in vivo*. This is perhaps somewhat surprising considering that previous studies, albeit essentially *in vitro*, have shown that both compounds are primarily absorbed by the paracellular route (6,7). Possibly, additional mechanisms are involved in the absorption of one or both compounds, or other factors unrelated to absorption are involved *in vivo*.

In summary, this study has shown that PEG 400 has a marked influence on the gastrointestinal absorption of ranitidine, particularly in terms of reducing bioavailability. This may be attributed to the accelerating effect of PEG 400 on small intestinal transit, although trans-mucosal fluid fluxes may also play a role. Furthermore, the appearance of double peaks in the pharmacokinetic profiles of ranitidine was less pronounced in the presence of PEG 400, and little or no correlation was observed between the absorption of the two compounds. More importantly, the results of the study call into question the use of PEG 400 as an inert solubility-enhancing vehicle. For those drugs that are primarily absorbed from the small intestine, these findings should be borne in mind when formulating with PEG 400.

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