The Effect of Different Concentrations of Mannitol in Solution on Small Intestinal Transit: Implications for Drug Absorption

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The aim of the present study was to investigate the effect that different concentrations of mannitol have on small intestinal transit, and whether any observed effect was concentration dependent. Eight, healthy male subjects each received 200ml of radiolabelled purified water, or a 200ml solution of mannitol at three different concentrations; 0.755g/200ml, 1.509g/200ml and 2.264g/200ml, in a randomised, four way cross-over study. Transit of the radiolabelled solutions was followed by gamma scintigraphy. The study demonstrated no significant differences between the gastric emptying times of the four solutions. Rapid gastric emptying was observed in most cases. The mean small intestinal transit times for the 0.755g/200ml, 1.509g/200ml and 2.264g/200ml mannitol solutions was reduced by 11%, 23% and 34% respectively, when compared to the control solution. The intestinal transit data of the four solutions demonstrate that mannitol has a concentration dependent effect on small intestinal transit. Small concentrations of mannitol included in a pharmaceutical formulation could therefore lead to reduced uptake with any drug exclusively absorbed from the small intestine.

KEY WORDS: mannitol; small intestinal transit; drug absorption; gamma scintigraphy.

INTRODUCTION

The oral route is the most popular and convenient route of drug administration for those compounds that can be absorbed across the gastrointestinal (GI) mucosa (1). The greater part of digestion and absorption takes place in the small intestine (SI), which consists of the duodenum (about 25cm long), the jejunum (approximately 2m) and the ileum (approximately 3m) (2). During the postprandial period, the SI undergoes peristaltic movements that propel the alimentary bolus, and segmental movements promoting mixing and dispersion (3). In the fasted state, the SI is swept by waves of the migrating myoelectric complex (MMC) (4). Despite these different mechanisms, the transit of various dosage forms in the SI is remarkably consistent with a mean transit time in the order of 3-4 hours (5,6). However, recent studies have shown that the inclusion of certain pharmaceutical excipients into the dosage form can have an effect on the small intestinal transit (SIT) time. For example, the incorporation of sodium acid pyrophosphate into an effervescent tablet, reduced SIT time by 43% (7), and xylitol another excipient in frequent use, has been also shown to reduce SIT time (8,9).

Mannitol is a white, odourless, crystalline powder, commonly used as a diluent or sweetening agent in oral dosage forms. Mannitol is poorly absorbed from the small intestine (10), 74% of a 10g oral load of mannitol has been recovered from the terminal ileum, after passing through the small intestine of patients with ileostomies (11). Urinary recovery following oral loading (27.5mmol in 100ml of water) has been shown to be 8.0-39.6% of the ingested amount (12). A laxative effect has been shown to occur with mannitol at a 'threshold dose' of 10 to 20g (13). Acceleration of SIT has been shown to occur with 150mmol/l oral loads of mannitol in solution (14,15), which resulted in decreased absorption of coadministered compounds (16). A recent study has shown that mannitol in solution can cause an acceleration of SIT at much lower concentrations than those used previously (14,15). A mannitol solution (2.264g/200ml), which is representative of concentrations used in pharmaceutical formulations, caused a 34% reduction in SIT time when compared to a control formulation (17). Increasing the rate of SIT reduces the time available for drug absorption and may contribute to impaired absorption of luminal contents. Therefore, the incorporation of an excipient like mannitol into a pharmaceutical formulation could lead to reduced bioavailability for drugs that are exclusively absorbed from the SI.

The aim of this study was to investigate the effect that mannitol has on SIT and whether this effect is concentration dependent. Gamma scintigraphy was used to follow the GI transit of Purified Water B.P. and three different concentrations of mannitol in solution.

MATERIALS AND METHODS

Subjects

The study was carried out in eight, healthy males (22-28 years) who were non-smokers and were not on any medication. Each volunteer gave written informed consent to participate in the study. The volunteers were not allowed to consume alcohol during the study period, or in the preceding 24 hours. The experimental protocol was approved by the ethics committee of the University of Nottingham and the study was conducted in accordance with the Declaration of Helsinki guidelines for ethics in research. Approval to administer the radiopharmaceuticals was obtained from the Department of Health, London, UK.

Radiolabelling of Dosage Forms

Three concentrations of mannitol; 0.755g, 1.509g, and 2.264g in 200ml of Purified Water B.P. were the test formulations. The control was 200ml of Purified Water B.P. alone. The test solutions were freshly prepared on each study day. Each 200ml aliquot of solution was radiolabelled with 4MBq

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of $^{99}Tc^{m}$ diethylenetriaminepentaacetic acid (DTPA) (<0.2ml).

Study Protocol

Each subject was studied on four separate occasions, at least 48 hours apart, in a four way randomised cross over study. On each of the study days, the subjects received the test solutions after an overnight fast. No additional food or fluid was allowed until 4 hours post dose, when the volunteers received a standard lunch (3800kJ).

Small $^{99}Tc^{m}$-labelled anatomical reference markers were taped to the skin anteriorly and posteriorly over the right lobe of the liver. Immediately after dosing, anterior and posterior images, each of 50s duration, were recorded approximately every 10min until all the labelled contents had reached the colon. The gamma camera (General Electrical Maxi-Camera) had a 40cm field of view and was fitted with a low energy parallel hole collimator. The images were recorded using a Bartec computer system and stored on magnetic tape for subsequent analysis.

Data Analysis

Each image was aligned with the anatomical reference markers. Dispersion of the solution enabled delineation of the stomach and colonic region, relative to the anatomical marker. Gastric emptying (GE) and colon arrival (CA) of the solution formulations was determined by identification of the stomach and colon anatomy from the series of acquired images. Regions of interest were constructed around the stomach and/or colon and the activity quantified. A further region of interest was drawn on each image, away from the main activity, to allow for the correction of background activity. The data were corrected for radioactive decay. The attenuation of the radiation by overlying tissues can give rise to incorrect estimates of the amounts of radioactivity in the regions of interest, however, this was overcome by calculating the geometric mean of the anterior and posterior counts, which gave a result that was relatively independent of the depth of the source (18). GE time was taken as the time for 50% of the solution to empty from the stomach, and CA was taken as the time for 50% to arrive in the caecum. SIT times were taken as the difference in time between 50% of the solution arriving in the colon and 50% of the solution leaving the stomach.

Statistical analysis was performed on the GE, CA and SIT times for the four solutions. A paired Student t-test ($p<0.05$) was used to compare the mannitol transit data, to that of the control preparation.

RESULTS

Gastrointestinal Transit of the Solutions

Following ingestion, the solution formulations rapidly dispersed throughout the stomach. GE began immediately in all volunteers, except in subject 6 after administration of the 1.509g/200ml solution, when onset of GE was delayed for 19min. The GE T50% times of the three mannitol solutions and purified water, are shown in Table I. The mean T50% times for the solutions ranged from 10 to 15min. There were no significant differences between the GE T50% times of the four solutions; (Control vs 0.755g/200ml, $p=0.433$; Control vs 1.509g/200ml, $p=0.180$; Control vs 2.264g/200ml, $p=0.225$).

The SIT data for the four solutions are provided in Table II. The T50% times for SIT of the control formulation were in the range of 188 to 423min, with a mean value of 258min and a median of 242min. The mean T50% times for SIT of the three mannitol solutions were; 0.755g/200ml - 230min; 1.509g/200ml - 199min; 2.264g/200ml - 170min. Although a few volunteers did not show an obvious decrease in SIT time in response to an increasing concentration of mannitol in solution, analysis of the group data by Page's L trend test showed the trend for SIT time to decrease with increasing mannitol concentration to be statistically significant at the 1% level ($L=226$). The mean T50% SIT times decreased as the concentration of mannitol in solution increased. Only the T50% transit time of the 2.264g/200ml solution was significantly different from that of purified water ($p = 0.016$). The 0.755g/200ml, 1.509g/200ml and 2.264g/200ml mannitol solutions reduced SIT times by 11%, 23% and 34% respectively, when compared to the control formulation. The mean SIT profiles for the four solutions are shown in Figure 1.

The CA data for the solutions (Table III), followed a similar trend to that of the SIT results. The 2.264g/200ml

Table I. Gastric Emptying Times (Minutes) for 50% of the Radiolabelled Solution Following Administration to Eight Fasted Male Volunteers

Volunteer number	Purified water B.P.	Mannitol 0.755g/200ml	Mannitol 1.509g/200ml	Mannitol 2.264g/200ml
1	11	5	15	12
2	12	10	10	14
3	10	8	10	12
4	8	26	12	8
5	7	8	6	5
6	8	8	39	6
7	16	20	18	22
8	5	9	12	8
Mean	10	12	15	11
SD	3	7	10	6
Median	9	9	12	10

Table II. Small Intestinal Transit Times (Minutes) for 50% of the Radiolabelled Solution Following Administration to Eight Fasted Male Volunteers

Volunteer number	Purified water B.P.	Mannitol 0.755g/200ml	Mannitol 1.509g/200ml	Mannitol 2.264g/200ml
1	244	233	125	200
2	242	240	242	233
3	244	236	152	127
4	242	222	235	227
5	242	247	230	173
6	239	201	156	124
7	423	231	212	169
8	188	235	240	111
Mean	258	230	199	171
SD	69	14	47	47
Median	242	234	221	171

mannitol solution T50% CA time was significantly different from that of the control information ($p = 0.016$), whilst the other two solutions showed no statistical significant differences in CA time compared to the control.

DISCUSSION

GE is a complex function because of the heterogeneity of gastric contents, and their physical, chemical and calorific properties. The main determinant of liquid emptying rate is volume; the rate is exponential, so that the volume emptied in unit time is proportional to the volume present (19). Emptying of neutral, iso-osmolar, and calorifically inert solutions is rapid (20). All the test solutions in the study were hypotonic compared to plasma, and had a low calorific load. GE of the solutions, as one would expect, was therefore rapid.

Unabsorbable disaccharides have been shown to cause pronounced movement of water and electrolytes into the lumen of the proximal SI (21, 22). Kern and Struthers (21) have observed that an electrolyte free lactose solution trebled in volume in a 100cm segment of SI and the contents throughout were iso-osmotic with plasma. The lactose in solution would only be contributing one third of the osmolality, with the majority being maintained by the sodium and chloride ions. Therefore, the resultant solution in the SI would behave very differently from the original lactose solution. The SI renders and keeps its contents isotonic (22, 23), and tends to equilibrate the sodium ion concentration in the lumen with plasma (23).

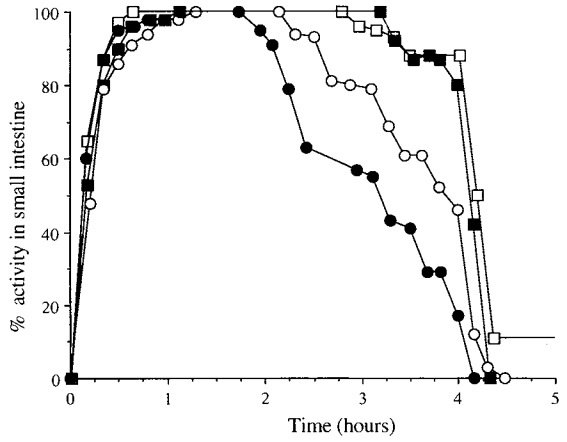

Fig. 1. Mean small intestinal transit profile for water and three different concentrations of mannitol solutions. —□— Purified Water B.P.; —■— Mannitol 0.755g/200ml Solution; —○— Mannitol 1.509g/200ml Solution; —●— Mannitol 2.264g/200ml Solution.

The duodenum is freely permeable to water, sodium ions and solutes. A solution emptying from the stomach will be made rapidly isotonic (23). Electrolyte free xylose solution has been shown to cause net secretion of water into the intestinal lumen (23). Xylose is poorly absorbed, thus plasma solutes enter the lumen more rapidly than xylose leaves, resulting in a net movement of solutes and water into the lumen (23). The mannitol solutions in the present study contained no sodium or chloride ions and were hypotonic. Therefore, on emptying from the stomach the solutions would become rapidly isotonic and due to the sodium ion concentration gradient between plasma and the solutions, one would expect the ions to diffuse into the lumen. This endeavour to achieve equilibrium leads to considerable binding of water and electrolytes in the SI. It is suggested that the mannitol may have bound sodium and chloride ions in the lumen, causing an osmotic gradient which results in water influx into the lumen. Therefore the resultant behaviour of the mannitol solution *in vivo* would be primarily dependent upon the sodium ion concentration and the influx of water into the lumen.

Fluid secretion and retention in the gut lumen distends the intestine, stimulates peristalsis (16) and generates propagative motor activity (24). Intubation studies have shown that low flow rates of an isotonic electrolyte solution through the small intestine (3-7 ml/min) cause an increase in the internal diameter of the small intestine without an acceleration of SIT. However, flow rates greater than 7ml/min appear to exceed the capacity of the small intestine to dilate and accommodate the extra volume, and instead a rapid transit time occurs (25). At low concentrations of solute 'loads' progressive accumulation of fluid may occur. Higher solute doses might, by inducing more vigorous initial fluid accumulation, trigger peristaltic acceleration of transit at a much earlier stage (16). Therefore, the lower the concentration of mannitol in solution the less the impact on SIT it will generate. In the present study it appears that the effect mannitol

Table III. Colon Arrival Times (Minutes) for 50% of the Radiolabelled Solution Following Administration to Eight Fasted Male Volunteers

Volunteer number	Purified water B.P.	Mannitol 0.755g/200ml	Mannitol 1.509g/200ml	Mannitol 2.264g/200ml
1	255	238	140	212
2	254	250	252	247
3	254	244	162	139
4	250	248	247	235
5	249	255	236	178
6	247	209	195	130
7	439	251	230	191
8	193	244	252	119
Mean	268	242	214	181
SD	72	15	44	49
Median	252	246	233	185

has on SIT time could be concentration dependent; the lower the concentration of mannitol in solution, the smaller its effect in decreasing SIT time.

Doses of mannitol as low as 0.755 - 2.264g can accelerate small intestinal transit and thus could be the cause of impaired absorption for drugs that are preferentially absorbed from the small intestine.

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