ELSEVIER

International Journal of Pharmaceutics 248 (2002) 61–70

international journal of pharmaceutics

www.elsevier.com/locate/ijpharm

The effect of ileal brake activators on the oral bioavailability of atenolol in man

Clair L. Dobson [a], Stanley S. Davis [a], Sushil Chauhan [b], Robert A. Sparrow [c], Ian R. Wilding [d,*]

[a] *Institute of Pharmaceutical Sciences, Nottingham University, Nottingham NG7 2RD, UK*
[b] *GlaxoSmithKline, New Frontiers Science Park, Harlow, Essex CM19 2AD, UK*
[c] *School of Biomedical Sciences, Queen's Medical Centre, Nottingham NG7 2UH, UK*
[d] *Pharmaceutical Profiles Ltd., Mere Way, Ruddington Fields, Ruddington, Nottingham NG11 6JS, UK*

Received 22 January 2002; received in revised form 1 July 2002; accepted 15 July 2002

Abstract

A study was carried out in human volunteers to investigate whether ileal brake activators could alter the bioavailability of atenolol from the small intestine by slowing intestinal transit and thereby increasing the time available for absorption. Oleic acid and a monoglyceride were formulated into modified release capsules that were targeted to the small intestine. Atenolol was either dosed separately or incorporated into one of the capsules. Radiolabelled non-disintegrating tablets were dosed at the same time in order to determine the small intestinal transit time (SITT). Plasma concentrations of atenolol were determined by HPLC. The results showed that in some volunteers an increase in SITT did lead to an increase in the quantity of drug absorbed. However, drug absorption was related not only to the total time spent by the drug in the small intestine but other factors such as the proportion of such time spent at the ileocaecal junction. The study highlights the complexities of exploiting natural gastrointestinal processes to enhance the oral bioavailability of drugs.

Keywords: Modified release; Ileal brake; Scintigraphy; Drug absorption

1. Introduction

As its name suggests, the ileal brake is literally a braking mechanism which acts to slow down the transit of luminal contents through the distal portion of the small bowel (Spiller et al., 1984; Lin et al., 1997). Originally it was considered as a response to the presence of excess dietary fat in the ileum (Brown et al., 1993; Dreznik et al., 1994), but it is now recognised that various nutrients are capable of eliciting such a response at different sites along the small intestine. Fats have been the most widely investigated materials selected as potential brake activators and various studies have demonstrated an effect on transit using fatty

* Corresponding author. Tel.: +44-115-974-9000; fax: +44-115-974-8000
E-mail address: iwilding@pharmprofiles.co.uk (I.R. Wilding).

0378-5173/02/$ - see front matter
PII: S0378-5173(02)00393-9

acids and other partial digests of lipids (Spiller et al., 1984, 1988). Although triglycerides have been shown to alter transit, larger effects seen with lipid hydrolysis products would suggest a greater sensitivity to fatty acids, mono- and di-glycerides (Spiller et al., 1988; Martinez et al., 1995). However, the ileal brake effect has also been seen when carbohydrate and protein substances are infused into the intestine suggesting a generalised activation process (Schemann and Ehrlein, 1986).

The absorption of nutrients can increase when intestinal transit is slowed since a delay in small bowel transit increases the contact between the luminal contents and the absorptive epithelium (Huge et al., 1995). Hence any activation of the ileal brake has the potential to increase intestinal absorption of drugs. An interesting observation is that the ileal brake does not slow transit throughout the whole small intestine; instead, the effect is localised to the distal ileum and to the transit of luminal contents across the ileocaecal junction (Hammer et al., 1998). Consequently, the absorption potential of the terminal ileum and ICJ is maximised.

Our previous work investigating the ileal brake in man (Dobson et al., 1999, 2000) has shown that the transit of non-disintegrating tablets through the small intestine can be slowed by the local activation of the brake mechanism. This effect on transit could have important consequences for drug delivery and absorption. If the residence time of an oral dosage form in the small intestine could be increased by exploitation of the ileal brake mechanism, there should be greater time available for drug absorption, which might lead to an increase in drug bioavailability. Therefore, the present study was designed to investigate whether an increase in the small intestinal transit time (SITT), caused by brake activators, could affect drug absorption. Previous investigations have shown that oleic acid and a proprietary mixture of monoglycerides (DMG-04) were effective brake activators when delivered to the ileum using modified release (MR) dosage forms.

The beta$_1$-adrenoreceptor antagonist, atenolol was chosen as a model drug in this study. Atenolol is incompletely absorbed from the gastrointestinal (GI) tract of man with the absorption ranging from 28 to 47% (Rigby et al., 1985). As it is a hydrophilic compound it is poorly absorbed from the colon (Rigby et al., 1985). A prolongation of small bowel transit following stimulation of the ileal brake mechanism should therefore enhance oral bioavailability.

2. Materials and methods

Atenolol of clinical grade was kindly donated by Cosma SPA (Bergamo, Italy). Starch capsules as described in the USP were obtained as a gift from West Pharmaceutical Sciences, Nottingham. A mix of monoglyceride (DGM-04) was obtained from Archer Daniels Midlands. Oleic acid was provided by William Ransom. Hard gelatin capsules, size 000 were obtained from Capsugel, Switzerland. Eudragit L100 and S100 were acquired from Rohm, Pharma, Darmstadt. Amberlite IRA-410 and IRP 69 resins were provided by Sigma (UK). Technetium-99m (^{99m}Tc) sodium pertechnetate was obtained from a generator system (Department of Medical Physics, Queen's Medical Centre, Nottingham). Indium-111 (^{111}In) available as the chloride was obtained from Nycomed Amersham. All other reagents were of reagent grade purity and were used as received.

2.1. Study design

Healthy volunteers ($n = 8$) were fasted from 22:00 h overnight before each study day. At approximately 08:00 h each subject was dosed with five tablets labelled with the gamma emitting radionuclide ^{111}In. The subjects were also dosed with one of the following formulations in a randomised order:

A) Starch capsule containing 50 mg atenolol (unlabelled).
B) Starch capsule containing 360 mg DMG-04 (labelled with ^{99m}Tc) and a starch capsule containing 50 mg atenolol.
C) Hard gelatin capsule (000) containing 600 mg DMG-04 and 50 mg atenolol (^{99m}Tc labelled).

D) 2 × Hard gelatin capsules (000) each containing 1200 mg oleic acid (^{99m}Tc) labelled) and a starch capsule containing 50 mg atenolol.

2.2. Capsule manufacture

Capsules containing 360 and 600 mg DGM-04 were manufactured for regimens B (starch capsule) and C (hard gelatin capsule), respectively. The capsule bodies were filled with the required amount of DMG and then the cap sealed to the body with cyanoacrylate adhesive. The hard gelatin capsules used in leg D were filled initially with 200 mg oleic acid before sealing as above. All capsules were coated, using a Niro Aeromatic coater, with a solution containing the enteric polymers Eudragit L100 and S100 (Watts, 1995). Once coated the capsules withstood disintegration in an acidic media and in vitro release commenced after 45–60 min when tested in a media at pH 6.8.

The capsules were radiolabelled the day before dosing by the addition of a ^{99m}Tc labelled Amberlite IRA-410 resin. A weight of resin, containing activity to give the required dose of radioactivity was added to the capsule through a hole drilled in the top of the capsule. The capsules used in leg D, had further oleic acid added at this point to provide a total of 1200 mg of oleic acid per capsule. The hole was then sealed with cyanoacrylate adhesive. The total amount of activity given in the test formulations at the time of administration was 4 ± 0.8 MBq (in leg D this was split between the two capsules).

The capsules containing only atenolol (as dosed in legs A, B and D), were prepared by weighing 50 mg atenolol into starch capsules which were then sealed with cyanoacrylate adhesive. The capsules were uncoated and as such allowed for the immediate release of the contents in the stomach. Atenolol was added to the capsule used in leg C at the same time as the radiolabelled resin.

2.3. Tablet manufacture

Placebo non-disintegrating tablets were prepared containing a ^{111}In label as described in detail previously (Khosla et al., 1989). Briefly Amberlite resin IRP-69 was radiolabelled by wetting with a solution of ^{111}In chloride and dried by heating at 60 °C. A quantity of resin, that would give the correct activity on dosing, was added to ethylcellulose and the mixture compressed to form 6 mm diameter tablets of weight 90–110 mg. The tablets were then coated to prevent disintegration in the GI tract with a mixture of ethylcellulose 4.5 g, acetylbutylcitrate 0.5 g, isopropanol 95.0 g followed by a mixture of cellulose acetate 10 g, methanol 18 g, dichloromethane 72 g. Five of the tablets were tested for disintegration in a stirred beaker for 24 h in pH 6.8 phosphate buffer. The coating remained intact and no radioactivity was released into the dissolution media. The approximate activity per tablet at the time of dosing was 0.2 MBq.

2.4. Volunteers

The study was undertaken in eight healthy non-smoking subjects who had undergone a medical examination to ensure they met protocol requirements. The protocol was approved by the University of Nottingham Medical School Ethics Committee. Volunteers were not allowed to take any medications during the study period and abstained from alcohol for 48 h prior to each study day.

2.5. Study day procedures

When dosing with Regimen A, B or C, the five ^{111}In labelled tablets were administered at the same time as the test articles. However, when dosing with formulation D, the subjects were initially dosed with two capsules containing oleic acid and were not given the other formulations (atenolol capsule and ^{111}In labelled tablets) until the gelatin capsules had reached the stomach. The progress of the capsules through the oesophagus was monitored in real time using a GE gamma camera fitted with a medium energy collimator. The volunteers remained sitting or standing for the duration of the study day. They received a standard lunch (1200 kJ) and tea (2400 kJ) at 4 and 9 h post-dose, respectively. From 10 h onwards unlimited fluids were available. At 14 h the volunteers ate supper. At 16 h post-dose the

Table 1
SITT (min) of preparations following oral dosing

Regimen					
Subject	A	B	C		D
	Control (no brake activator)	360 mg DMG-04 (atenolol dosed separately)	600 mg DMG-04 and 50 mg atenolol		2400 mg oleic acid (atenolol dosed separately)
			Tablets	Capsule	
1	359	291	674	351	436
2	191	399	345	244	>476
3	166	170	241	267	232
4	252	228	216	207	139
5	202	248	443	399	78
6	130	96	214	74	50
7	175	211	97	136	143
8	198	108	283	228	92

volunteers were allowed home, returning at 24 h post-dose for a final blood sample.

On each study day, before dosing, a cannula was inserted into an arm of each volunteer through which blood samples were obtained. Patency of the cannula was maintained by flushing with heparinised saline. Blood samples were obtained from the volunteers at the following nominal times post-dose; 0, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 7, 8, 10, 12, 16 and 24 h.

Before dosing an external marker, labelled with ^{111}In was positioned on the volunteer's abdomen, over the right lobe of the liver. Anterior images, each of 60 s duration, were collected using the gamma camera, at approximately 10–15 min intervals throughout the study day until approximately 10 h post-dose. The position of the dosage forms was then assessed in real time and if the preparations were all in the colon then no further imaging was carried out. If the formulations were still in a more proximal region of the GI tract then imaging was continued until all dosage forms had entered the colon.

2.6. Image analysis

The use of the external marker, which remained fixed for the entire study day, allowed the relative positions of the tablets and capsule to be determined for each image. By viewing consecutive images it was possible to define the different anatomical regions of the GI tract (stomach, small intestine or colon) and therefore to determine the position of the dosage forms and when they moved from one region to another. The times quoted for gastric emptying (GE) and colon arrival (CA) are the mid-point of the times of the images between which the events occurred. Once the GE and CA values of each of the five tablets was determined the mean value of both events was calculated. The difference between the two values was taken to be the SITT. Analysis of the images was undertaken by investigators skilled in data assessment.

2.7. Analysis of plasma samples for atenolol concentration

The plasma samples were analysed for atenolol using a previously validated HPLC method. Briefly the assay consisted of the isolation of atenolol and internal standard from alkalinised human plasma by solvent extraction. The sample was mixed with 2 M sodium hydroxide before undergoing extraction with cyclohexane–butan-1-ol (55:45, v/v). The analytes were then back-extracted into dilute sulphuric acid and the organic phase removed. The acid was alkalinised with further 2 M sodium hydroxide and the analytes

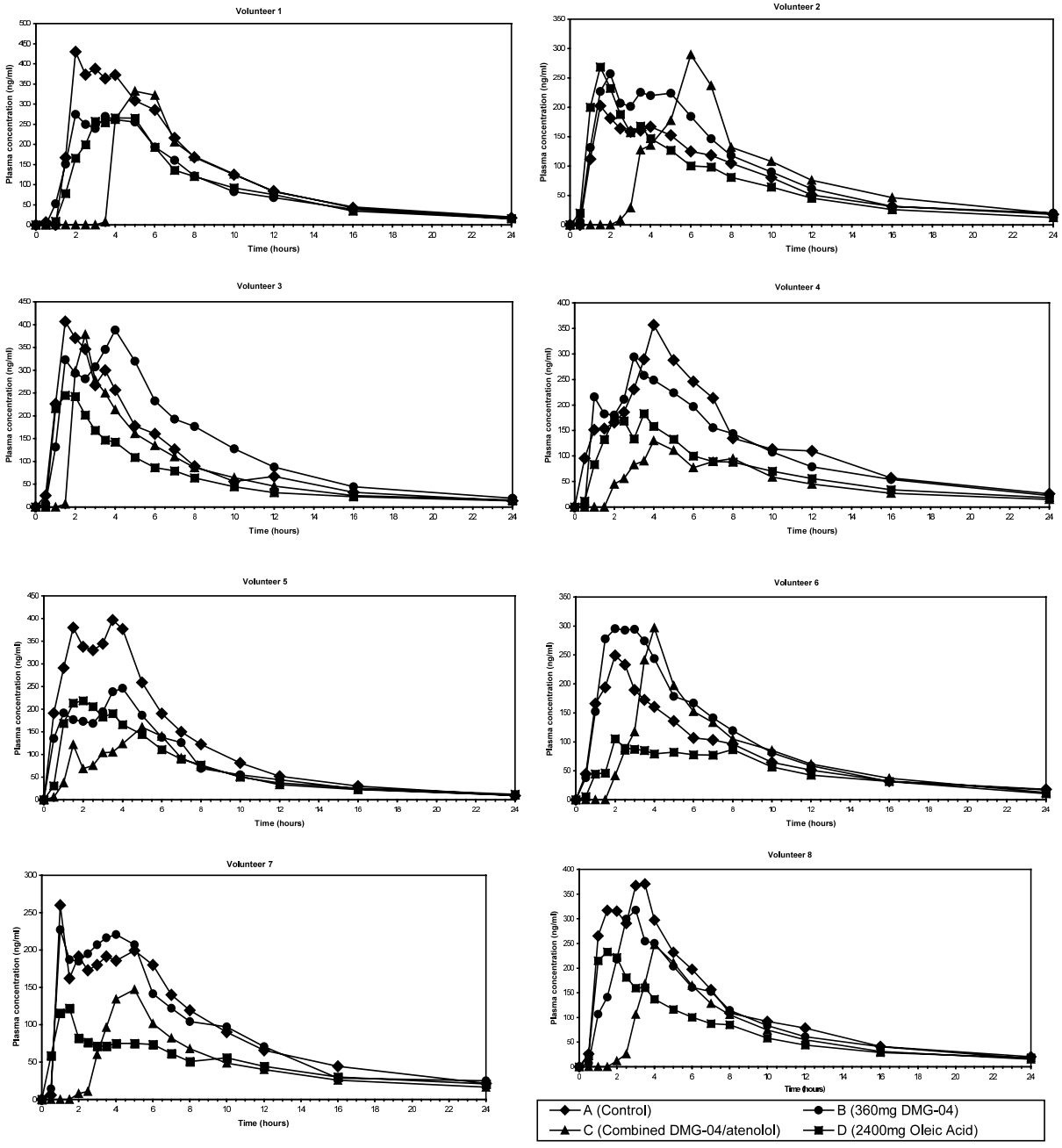

Fig. 1. Plasma atenolol concentrations for each volunteer.

extracted in to methyl-*tert*-butyl ether. The organic phase was removed and then evaporated under nitrogen. The analytes were then reconstituted in a small volume of mobile phase and a portion of this was analysed on a μBondapak C18 analytical HPLC column in the reverse phase

Table 2
Proportion (%) of SITT spent at ICJ following oral dosing

Regimens				
Subject	A	B	C	D
	Control	360 mg DMG-04 (atenolol separate)	600 mg DMG-04 and 50 mg atenolol	2400 mg oleic acid (atenolol separate)
1	33	47	81/79/79	78
2	52	72	30/24/43	77
3	69	69	41/71/100	57
4	37	18	39/41/64	18
5	77	64	93/95/97	72
6	60	75	19/43/100	10
7	77	75	8/Not calculable	0
8	91	57	68/73/85	Not calculable

The percentage of time spent at ICJ was calculated as follows:

For Regimens A, B and D—percentage of SITT spent at ICJ

$$= \frac{\text{difference between time of CA and time for ICJ arrival for tablets} \times 100}{\text{SITT of tablets}}.$$

For Formulation C three values are provided. The first value is calculated in the same way as those for A, B and D i.e. the percentage time at ICJ for the tablets. The second and third values apply to the MR capsule.

The second value—% of SITT of capsule spent at ICJ

$$= \frac{\text{difference between time of CA and time for ICJ arrival for capsule} \times 100}{\text{SITT of capsule}}.$$

The third value—% of post-capsule disintegration SITT spent at ICJ

$$= \frac{\text{difference between time of CA and time for ICJ arrival for capsule} \times 100}{\text{difference between time of CA and time of capsule disintegration}}.$$

mode with the eluent monitored by fluorescence detection at 280 (excitation) and 300 nm (emission). Each batch of test samples were analysed along with a set of calibration standards and independently prepared quality control samples at low, intermediate and high concentrations over the validated concentration range.

3. Results and discussion

Table 1 shows the SITT of tablets for each regimen plus the SITT of the capsule dosed in regimen C for each volunteer. The proportion of the total SITT spent at the ICJ are provided in Table 2 as percentage figures. Fig. 1 shows the plasma atenolol concentrations for each volunteer and the respective AUCs are provided in Table 3.

It was anticipated that the SITT of the placebo tablets would increase when dosed with a brake activator. As can be seen from Table 1 in nearly 50% of cases the SITT was increased with the test regimens compared to the control. The most notable examples are seen for volunteers 1 and 2 who showed increases from 359 and 191 min to 674 and 345 min, respectively, when dosed according to regimen C. Interestingly, a trend was observed in this work which was unexpected. In four volunteers the dosing of oleic acid in formulation D actually led to more rapid small bowel residence time (SITT); three volunteers showing a halving of SITT. This was opposite to an expected

increase in SITT. It was apparent that either the ileal brake was not being activated or that the braking action was masked by some other effect that was speeding up transit. One possible reason for this result could be the local action of oleic acid on the intestinal mucosa. Previously, we have shown that oleic acid at doses up to 1200 mg can activate the ileal brake (Dobson et al., 1999). The choice of 2400 mg in the present study was to ensure that enough oleic acid was delivered to the small intestine to exceed any threshold level for activation. Such a large dose should have acted as a positive control. However, it appears that the use of such a dose of oleic acid does not only stimulate the ileal brake, but additionally presents the small intestine with a large highly localised quantity of a potentially irritant fatty acid. We believe that the net increase in transit in the small intestine when using high doses of oleic acid may be caused by a purgative effect. It is known that certain substances e.g. triglyceride of ricinoleic acid (present in castor oil) form products in the small intestine which cause irritation to the mucosal wall hastening the passage of bowel contents (Davis et al., 1988). The dose of oleic acid administered could have been acting as a physical irritant, causing a response which overcame the braking mechanism and thereby accelerated transit. An analysis of the SITT results shows that the expected slowing of transit time was obtained with formulation C, containing a 600 mg dose of the monoglyceride mix, DMG-04. A lower dose of 360 mg of DMG-04 in formulation B did not have an effect on tablet transit.

The results for SITT are the values for the total time spent within the small intestine and as such, do not give an indication of the pattern of the transit; namely the proportion of time spent by the product in the different areas of the small bowel. Although the technique of gamma scintigraphy is useful for determining movement between the different areas in the GI tract, it has limited value in differentiating between the different small intestinal regions. This is due to the convoluted nature of the small intestine, which prevents a complete anatomical definition. However, it was possible to differentiate clearly the last segment of the small intestine; the ileo-caecal junction (ICJ). Therefore, values can be quoted for the proportion of the SITT spent at ICJ (Table 2). For the formulations where atenolol was dosed separately (i.e. legs A, B and D), the values given were simply calculated from the tablet data. The situation with formulation C is more complex since the atenolol was dosed in the test capsule itself and therefore was not available for absorption until this capsule had begun to disintegrate. However, the test capsules were radiolabelled and data for the time spent at the ICJ were available, thus allowing the transit behaviour of the 'drug' to be assessed.

The primary aim of the present study was to determine if the absorption of atenolol was affected by the ileal brake mechanism by reviewing of the pharmacokinetic and transit data. The plasma concentration versus time profiles show some interesting results, which do not immediately appear to correspond with the GI transit data. The expected trend was that an increase in SITT should provide a corresponding increase in the absorption of atenolol and hence a greater AUC. However, from a consideration of all the SITT and AUC data, such a general trend was not observed. Consequently, it is necessary to consider the complete set of scintigraphic and pharmacokinetic data for each volunteer; Table 4 summarises these main findings from each subject.

The ICJ has a valve-like function controlling the input of food material (chyme) into the colon. It is not considered to be a good site for the efficient absorption of drug, possibly contributing to the lower than anticipated AUC. Reduction in drug absorption has been shown previously with oxprenolol (a drug normally well absorbed from the whole of the GI tract) when delivered in a MR formulation undergoing stagnation (at the hepatic and splenic flexures) (Davis et al., 1988). If the time spent at the ICJ is an important factor in determining drug absorption this could have led to lower plasma levels than expected.

The plasma concentrations seen for subject 5 were unique, containing double peaks. Atenolol is not a drug normally associated with double peak phenomenon (Sabanathan et al., 1987; Sowinski et al., 1995). Such an event usually occurs due to enterohepatic recycling or bile excretion leading to what is essentially a second dosing of the GI tract

Table 3
Area under the curve (AUCs) (ng/ml h) for plasma profiles following atenolol dosing

Regimen				
Subject	A	B	C	D
	Control	360 mg DMG-04 (atenolol separate)	600 mg DMG-04 and 50 mg atenolol	2400 mg oleic acid (atenolol separate)
1	3074	2272	2162	2132
2	1743	2159	1887	1645
3	2344	3009	1780	1463
4	2853	2515	1130	1600
5	2738	1804	1235	1604
6	1783	2256	1732	1132
7	2148	2089	1057	1149
8	2696	2207	1565	1624

Table 4
Summary of main pharmacokinetic findings for each subject

Volunteer number	Summary of findings
1	AUC highest in control. Substantial increase in SITT with C and D does not cause increased AUC. Formulation B showed expected decrease in SITT leading to decrease in AUC
2	SITT of tablets was increased to the greatest extent in this volunteer. With formulation B AUC was also increased. Regimen C showed a comparable AUC to control; but the capsule SITT was not as great as that for tablets. Formulation D also did not increase AUC from control
3	With regimen B there was a large increase in AUC from control, despite a similar SITT and % time spent at ICJ. Unusual concentration profile with C_{max} occurring 2 h after tablets have emptied into colon, suggesting the capsule remnants, containing a reservoir of drug, remain in the absorptive small intestine for longer. With formulation C an increase in both capsule and tablet SITT was observed but AUC decreased
4	Control and formulation B gave similar AUC and SITT values. Regimen D provided a decrease in SITT, which correlated with decreased AUC. Formulation C decreased AUC, without significantly changing SITT or time at ICJ
5	Uniquely, amongst these volunteers, the plasma concentration profiles showed double peaks with the second peak being higher. Regimen D decreased both AUC and SITT. Formulation C increased SITT of the tablets by over 100% with a similar value for the capsule, but AUC was the lowest measured in this subject. Regimen B showed reduced AUC despite having SITT and time at ICJ values similar to control
6	Formulation D showed an exceptionally rapid SITT, 50 min, and a predictable decrease in AUC. Regimen B gave a slight decrease in SITT but an increase in AUC, possibly caused by the capsule remaining in the small intestine longer than the tablets. Formulation C increased tablet SITT but a faster capsule SITT, and longer residence at the ICJ (where capsule disintegration occurred) decreased AUC
7	Regimens A and B gave similar results; the test leg having no effect on either transit or drug absorption. Formulation C decreased both transit and absorption. Regimen D decreased both SITT and AUC, absorption being lower than expected from consideration of transit alone
8	SITT and AUC were both reduced with both formulation B and D, but with Regimen B the test capsule did not disintegrate until three tablets had entered the colon. Regimen C produced an increase in tablet SITT but a smaller increase in capsule SITT; a decrease in AUC, was possibly caused by 85% of the SITT occurring at the ICJ

with drug. Another explanation could be the presence of the two different sites with absorptive capacity within the GI tract for atenolol, the first being in the duodenum or upper jejunum, with the second more distally in the ileum. It is known that certain drugs have this type of absorption window leading to a double peak (Lennernas and Regardh, 1993) but it has not been shown to occur previously with atenolol.

4. Conclusions

When considering the results obtained for all the subjects, it is clear that there is no straightforward relationship between small intestine transit time and the absorption of atenolol. In most cases, drug absorption appears to be dependent on the time spent in the upper small intestine *and* the proportion of time spent at the ICJ; an increase in the former leads to greater absorption whereas an increase in the latter appears to decrease the absorption. As expected, absorption from the specialised region of the ICJ is not as great as that from other areas of the small intestine.

Our studies to date have suggested that the ileal brake works by increasing the time spent in the terminal ileum and at the ICJ (Dobson et al., 1999, 2000). This will increase the total transit time through the small intestine but not necessarily the time the drug spends at preferential sites of absorption in the upper small intestine. When some subjects were dosed according to regimen C, which contained both drug and DMG-04, the capsule did not disintegrate until it reached the ICJ, thus allowing no opportunity for absorption at other sites within the small bowel. Any drug transferred into the colon would be expected to be poorly absorbed (Rigby et al., 1985).

It is interesting that the absorption of the drug was not increased when dosed under regimen D and in seven of the subjects was substantially decreased. It seems possible that the dose of oleic acid employed may have prevented the absorption of the drug. Indeed it has been shown by others that oleic acid can have an inhibitory effect on the permeability of tight junctions; the route by which atenolol is absorbed (Lavado et al., 1997).

We conclude that ileal brake activators can sometimes influence drug behaviour in the GI tract and that these could have advantages for drugs absorbed in the distal ileum or having a local effect in the small bowel. However, it is clear that the exploitation of a natural process to enhance the bioavailability of drugs will not be straightforward. In addition, this study has demonstrated the important role of gamma scintigraphy in assessing the interaction of a potential drug delivery system and GI physiology.

References

Brown, N.J., Horton, A., Rumsey, R.D.E., Read, N.W., 1993. Granisetron and ondansetron: effects on the ileal brake mechanism in the rat. J. Pharm. Pharmacol. 45, 521–524.

Davis, S.S., Washington, N., Parr, G.D., Short, A.H., John, V.A., Lloyd, P., Walker, S.M., 1988. Relationship between the rate of appearance of oxprenolol in the systemic circulation and the location of an oxprenolol Oros 16/260 drug delivery system within the gastrointestinal tract as determined by scintigraphy. Br. J. Clin. Pharmacol. 26, 435–443.

Dobson, C.L., Davis, S.S., Chauhan, S., Sparrow, R.A., Wilding, I.R., 1999. The effect of oleic acid on the human ileal brake and its implications for small intestinal transit of tablet formulations. Pharm. Res. 16, 92–96.

Dobson, C.L., Davis, S.S., Chauhan, S., Sparrow, R.A., Wilding, I.R., 2000. Does the site of intestinal delivery of oleic acid influence its effect on the ileal brake? Int. J. Pharm. 195, 63–70.

Dreznik, Z., Meininger, T.A., Barteau, J.A., Brocksmith, D., Soper, N.J., 1994. Effect of ileal oleate on interdigestive intestinal motility of the dog. Dig. Dis. Sci. 39, 1511–1518.

Hammer, J., Hammer, K., Kletter, K., 1998. Lipids infused into the jejunum accelerate small intestinal transit but delay ileocolonic transit of solids and liquids. Gut 43, 111–116.

Huge, A., Weber, E., Ehrlein, H.-J., 1995. Effects of enteral feedback inhibition on motility, luminal flow and absorption of nutrients in proximal gut of minipigs. Dig. Dis. Sci. 40, 1024–1034.

Khosla, R., Feely, L.C., Davis, S.S., 1989. Gastrointestinal transit of non-disintegrating tablets in fed subjects. Int. J. Pharm. 53, 107–117.

Lavado, E., Sanchez Abarca, L.I., Tabernero, A., Bola os, J.P., Medina, J.M., 1997. Oleic acid inhibits gap junction permeability and increases glucose uptake in cultured rat astrocytes. J. Neurochem. 69, 721–728.

Lennernas, H., Regardh, C.-G., 1993. Evidence for an interaction between the β-blocker pafenolol and bile salts in the intestinal lumen of the rat leading to dose-dependent oral

absorption and double peaks in the plasma concentration–time profile. Pharm. Res. 10, 879–883.

Lin, H.C., Zhao, X., Wang, L., 1997. Intestinal transit is more potently inhibited by fat in the distal (ileal brake) than in the proximal (jejunal brake) gut. Dig. Dis. Sci. 42, 19–25.

Martinez, V., Jimenez, M., Gonalons, E., Vergara, P., 1995. Intraluminal lipids modulate avian gastrointestinal motility. Am. J. Phys. 269, R445–R452.

Rigby, J.W., Scott, A.K., Hawksworth, G.M., Petrie, J.C., 1985. A comparison of the pharmacokinetics of atenolol, metoprolol, oxprenolol and propranolol in elderly hypertensive and young healthy subjects. Br. J. Clin. Pharmacol. 20, 327–331.

Sabanathan, K., Castleden, C.M., Adam, H.K., Ryan, J., Fitzsimons, T.J., 1987. A comparative study of the pharmacokinetics and pharmacodynamics of atenolol, hydrochlorothiazide and amiloride in normal young and elderly subjects and elderly hypertensive patients. Eur. J. Clin. Pharmacol. 32, 53–60.

Schemann, M., Ehrlein, H.-J., 1986. Postprandial patterns of canine jejunal motility and transit of luminal contents. Gastroenterology 90, 991–1000.

Sowinski, K.M., Forrest, A., Wilton, J.H., Taylor, A.M., Wilson, M.F., Kazierad, D.J., 1995. Effect of ageing on atenolol pharmacokinetics and pharmacodynamics. J. Clin. Pharmacol. 35, 807–814.

Spiller, R.C., Trotman, I.F., Higgins, B.E., Ghatei, M.A., Grimble, G.K., Lee, Y.C., Bloom, S.R., Misiewicz, J.J., Silk, D.B.A., 1984. The ileal brake inhibition of jejunal motility after ileal fat perfusion in man. Gut 25, 365–374.

Spiller, R.C., Trotman, I.F., Adrian, T.E., Bloom, S.R., Misiewicz, J.J., Silk, D.B.A., 1988. Further characterization of the 'ileal brake' reflex in man—effect of ileal infusion of parial digest of fat, protein and starch on jejunal motility and release of neurotensin, enteroglucagon and peptide YY. Gut 29, 1042–1051.

Watts, P.J., 1995. Colonic drug delivery composition. International Patent A61K9/48, 28 December.