Jejunal and ileal absorption of oxprenolol in man: influence of nutrients and digestive secretions on jejunal absorption and systemic availability

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1 Study I evaluated the absorption of oxprenolol in the ileum, compared to jejunum, in healthy volunteers by an intestinal perfusion technique. Around 80 mg of drug were delivered as a saline solution directly in the small bowel.

2 Samples taken 30 cm distally to the site of perfusion showed that 63% of perfused oxprenolol was absorbed in the jejunum and 48% in the ileum; the differences were significant.

3 The plasma concentration-time profiles were similar for the two perfusions. The AUC and $C_{\max}$ values of free and conjugated oxprenolol for the jejunal perfusion were significantly lower than those of ileum. They showed large but consistent intersubject variations in the two treatments.

4 Study II investigated, using the same technique, the influence of nutrients and digestive secretions on jejunal absorption and systemic availability of this drug. A saline (in treatments A and B) or a nutrient (in treatment C) solution containing oxprenolol was perfused into the jejunum below a balloon either inflated (A) or deflated (B and C).

5 The disappearance rate of oxprenolol from the jejunum was unaffected by endogenous secretions. The mean amount of drug absorbed along a 30-cm jejunal segment accounted for 52 (A) and 57% (B) of the total amount perfused. The intestinal absorption rate was markedly increased in the presence of nutrients (mean amount absorbed 96% for C).

6 The change in the rate of disappearance from the intestine had no effect on the systemic availability of oxprenolol (mean AUC values 8740, 8250 and 8020 nmol l⁻¹ h for A, B and C, respectively) or its elimination from plasma.

7 The present findings and those obtained previously by intubation and colonoscopic techniques indicate that oxprenolol is not absorbed in the stomach but is absorbed all along the small and large intestines.

Keywords drug absorption oxprenolol ileum jejunum food

Introduction

The potential advantages of rate-controlled dosage forms with extended duration of release may be compromised by poor or unpredictable absorption in some regions of the intestine. An

acceptable and reproducible systemic availability from such dosage forms can only be achieved if drug absorption is relatively uniform throughout the greater part of the gastrointestinal tract.

During the development of osmotically-controlled drug delivery systems (Theeuwes *et al.*, 1985) for the β -adrenoceptor blocker oxprenolol, studies were designed to characterize absorption of this drug throughout the human gut.

The absorption of oxprenolol in the stomach and the upper small intestine, after administration of the drug with a meal, has been investigated by an intubation method (Vidon *et al.*, 1986), which demonstrated that the drug is absorbed similarly in the duodenum and in the upper jejunum, but not in the stomach.

The present two studies completed our investigations of oxprenolol absorption in the gastrointestinal tract.

Study I evaluated oxprenolol absorption in the ileum by comparison to jejunum, the drug being delivered as a saline solution directly in the small bowel.

Study II investigated whether, despite the reported lack of effect on the plasma concentrations (Dawes *et al.*, 1979; John & Smith, 1985), food affects oxprenolol disappearance from the intestine. For this purpose, a saline or a nutrient solution containing oxprenolol was perfused into the jejunum of volunteers.

Methods

Subjects

Fourteen (six in Study I, eight in Study II) healthy male volunteers, with no evidence or history of gastrointestinal or cardiovascular disease, were selected. They were asked not to take any drug for 8 days before and none other than oxprenolol during the experiment. They were advised not to smoke during the trial. They signed an informed consent form.

On each day of Study II, the subjects remained fasting for 12 h before and throughout the perfusion period.

Drug solution

Two solutions containing the same amount of oxprenolol hydrochloride (130 mg l^{-1}) were perfused at a rate of 5 ml min^{-1} during 2 h (theoretical dose 78 mg) in the form of: (a) a saline solution (Studies I and II) containing NaCl 130 mmol l^{-1} , KCl 5 mmol l^{-1} , mannitol 30 mmol l^{-1} , PEG 4000 5 g l^{-1} (total osmolality 300 mosm kg^{-1}). (b) a nutrient solution (Study II) comprising a homogenized liquid meal (Rea-mentyl®, Sopharga Laboratories) and water

together with NaCl 100 mmol l^{-1} , and PEG 4000 5 g l^{-1} . NaCl was added to get a solution with an osmolality of 300 mosm kg^{-1} . The caloric value was 1.3 kcal ml^{-1} .

Procedure

In both studies, oxprenolol absorption was evaluated in an intestinal segment by a perfusion technique using polyethylene glycol 4000 (PEG) as a water soluble, non absorbable marker (Modigliani *et al.*, 1973).

For each study, in the afternoon of the first day, the subjects were intubated with a four-lumen tube incorporating an occlusive balloon as previously described (Vidon *et al.*, 1985). This balloon, once inflated, prevented secretions (salival, gastric, biliary, pancreatic and intestinal) from reaching the intestinal segment under investigation. Immediately proximal to the balloon, a tube allowed a continuous aspiration of the luminal content. The infusion tube opening was immediately distal to the balloon. The aspiration site was 30 cm distally to this opening.

On each of the following days, a different procedure was applied in the two studies.

Study I In the morning of the second day, the perfusion point (checked radiologically) was positioned beyond the duodeno-jejunal junction (angle of Treitz). The saline solution was perfused after inflation of the balloon. Its occluding effect was checked with bromosulfophthalein, introduced above the balloon, with sampling at the aspiration site. The balloon was deflated at the end of the perfusion period. The tube was maintained in the gastrointestinal tract during the rest of the day and overnight.

On the third day, the perfusion point was positioned in the middle part of the ileum and the same procedure was followed.

Study II In the morning of the 3 days following the intubation, the perfusion site was positioned at the duodeno-jejunal junction and one of the following experiments described below was performed.

Experiment A: The balloon was inflated with air. Gastrointestinal secretions collected above the balloon were cleared by continuous aspiration. The saline solution was perfused.

Experiment B: The balloon was not inflated, allowing gastric, biliary and pancreatic secretions to enter the test segment. The saline solution was perfused.

Experiment C: As experiment B but nutrient solution was perfused.

In each study, the intraluminal fluid was aspirated continuously at a rate of 1 ml min^{-1} . After a 60 min equilibration period, six successive 10 min samples of intestinal fluid were obtained. Blood samples were collected before and at selected times over 8 h after the start of drug perfusion. Intestinal and plasma samples were stored at -20°C until analysis.

Analytical methods

PEG 4000 in each intestinal sample was measured by a turbidimetric method (Hyden, 1955).

H.p.l.c. methods were used to assay unchanged oxprenolol in intestinal fluid (Vidon *et al.*, 1986) and plasma (Godbillon & Gosset, 1985). The limits of quantitation (defined as the lowest concentration recovered with a coefficient of variation not exceeding 10%) were respectively $1 \mu\text{g ml}^{-1}$ in intestinal fluid, 20 ng ml^{-1} (66 nmol l^{-1}) in plasma.

The h.p.l.c. method used for the assay of total (free + conjugated) oxprenolol in plasma was derived from that for the unchanged drug (Godbillon & Gosset, 1985). Plasma was incubated at 37°C for 17 h with an aqueous solution at pH 5.2 of β -glucuronidase + aryl-sulphatase. After addition of alprenolol as internal standard, the aqueous phase was washed with dichloromethane. The compounds were extracted at alkaline pH into an organic phase and back-extracted into an acidic aqueous phase. Separation of the plasma components was achieved on a reversed-phase column. The limit of quantitation was 200 ng ml^{-1} (660 nmol l^{-1}).

The concentrations of conjugated oxprenolol were the differences between the concentrations found with (total) and without (free) hydrolysis.

Calculations and statistical analysis

The amount of oxprenolol absorbed in the 30 cm intestinal segment was calculated as previously described (Vidon *et al.*, 1985), as the difference between the amount entering and that recovered at the sampling site.

The net water movements were estimated from the difference between flow rates at the sampling and the perfusion sites. Negative values correspond to water absorption in the segment, positive ones to water secretion (Vidon *et al.*, 1985). The values given for these two parameters are the means of individual values calculated as means of six values obtained for each subject during the last hour of perfusion.

The amount of drug perfused in each subject was calculated from the concentration of oxprenolol measured in the perfusate and the actual

flow rate of perfusion for each individual. The actual dose (amount available for absorption) was the amount perfused minus the amount sampled. As it was not identical for each subject and each treatment (range 71.5 to 88.6 mg in Study I, 72.2 to 85.5 mg in Study II), the plasma concentrations measured were normalized to a 80 mg dose.

The areas under the plasma concentration-time curves (AUC) were calculated by the trapezoidal rule over the sampling period.

Plasma AUC and C_{max} , intestinal absorption rates were compared by two-way variance analysis, *t*-test for paired or unpaired values.

Results

Study I

Jejunum and ileum The amount of drug absorbed, in percent of the amount perfused, along each intestinal segment was significantly different ($P = 0.036$) in the two regions: 63% in the upper jejunum, 48% in the middle ileum. The inter-subject variability was comparable for the two segments (Table 1).

As a mean, there was a slight absorption of water (0.1 ml min^{-1}) during either perfusion (Table 1).

Plasma The plasma concentration profiles of free oxprenolol were similar after jejunal and ileal perfusion (Figure 1). As indicated by the magnitude of the standard error of the means, the AUC and C_{max} values showed large inter-subject variability (Table 1), similar for the two sites of perfusion. They were significantly different ($P = 0.027$ and $P = 0.011$, respectively) in the two treatments. The ratio ileum/jejunum ranged from 1.02 to 1.30 for AUC (mean 1.17), from 1.05 to 1.21 for C_{max} (mean 1.11).

The maximum concentration (C_{max}) was observed at the end of the perfusion either in jejunum or ileum for two subjects. For the other four, the peak occurred 0.5 h later.

Jejunal and ileal perfusions resulted in comparable plasma level-time curves for conjugated oxprenolol (Figure 1). The intersubject variability was similar for the two treatments. AUC but not C_{max} values (Table 1) were significantly different ($P = 0.044$ and $P = 0.058$, respectively). The mean ratio ileum/jejunum was 1.12 for AUC, 1.24 for C_{max} .

Study II

Jejunum The jejunal disappearance rates of oxprenolol were not significantly different ($P =$

Table 1 Study I: net water movements, oxprenolol absorption along a 30 cm segment of intestine and pharmacokinetic parameters of free and conjugated oxprenolol after perfusion of the drug in jejunum or ileum as a saline solution (mean values, $n = 6$, with s.e. mean or median)

Parameter	Jejunum	Ileum	Statistical analysis
Water movements [†] (ml min ⁻¹)	-0.1 (0.2)	-0.1 (0.2)	—
Oxprenolol absorbed in % of amount perfused	63 (6)	48 (4.5)	S
AUC (μmol l ⁻¹ h)			
free	6.3 (1.3)	7.3 (1.3)	S
conjugated	12.3 (2.3)*	13.8 (2.5)*	S
C _{max} (μmol l ⁻¹)			
free	1.7 (0.3)	1.9 (0.3)	S
conjugated	2.8 (0.4)*	3.5 (0.5)*	NS
t _{max} (h)			
free	2.5	2.5	—
conjugated	3.0	3.5	—

AUC, area under the plasma concentration-time curve over 8 h.

C_{max}, peak concentration.

t_{max}, time to C_{max}.

†, — = absorption.

*, $n = 5$, otherwise $n = 6$.

S, NS, significant, non significant difference (see text).

Figure 1 Mean plasma concentrations of free and conjugated oxprenolol after perfusion of a saline solution of the drug in jejunum (●) or ileum (□).

0.50) in treatments A and B: 52 and 57%, respectively, of the amount of oxprenolol perfused were absorbed along the segment (Table 2). When oxprenolol was perfused with nutrients (C), it was almost completely absorbed (96%) in 30 cm of intestine.

As a mean, a slight absorption of water (0.2 ml min⁻¹) was observed in experiment A. In experiment B where the balloon was deflated, water appeared to be secreted, i.e. secretions were not reabsorbed and were contributing to the perfusate. When the nutrient rather than the saline solution was perfused with the balloon deflated (experiment C), water absorption occurred, i.e. secretions and part of the perfusate were absorbed.

Plasma The plasma concentration profiles of oxprenolol were similar in experiments A, B and C (Figure 2). AUC and C_{max} values (Table 2) showed a large inter-subject variation which was similar with the saline (experiments A and B) and nutrient (experiment C) solutions. AUC values were not significantly different in the three treatments ($P = 0.61$). In experiments A and B, C_{max} occurred mostly 30 min after the end of the perfusion, i.e. at 2.5 h. In experiment

Table 2 Study II: net water movements, absorption along a 30 cm segment and pharmacokinetic parameters of oxprenolol perfused in the jejunum in a saline (A and B) or a nutrient solution (C) below a balloon either inflated (A) or deflated (B and C) (mean values with s.e. mean or medians)

	Experiment		
	A	B	C
Number of subjects	7	8	8
Water movements† (ml min ⁻¹)	-0.2 (0.3)	+1.2 (0.3)	-2.1 (0.4) ^a
Oxprenolol absorbed in % of amount perfused	52 ^b (5)	57 ^b (3)	96 (1)
AUC (μmol l ⁻¹ h)	8.7 ^c (1.4)	8.3 ^c (1.3)	8.0 ^c (1.3)
C _{max} (μmol l ⁻¹)	2.5 (0.4)	2.3 (0.3)	2.5 (0.3)
t _{max} (h)	2.5	2.5	2.0

AUC, area under the plasma concentration-time curve over 8 h.

C_{max}, peak concentration.

t_{max}, time to C_{max}.

†, + = secretion, - = absorption.

^a, n = 7.

^b or ^c, values not significantly different.

Figure 2 Mean plasma concentrations of oxprenolol after jejunal perfusion of the drug in a saline (A and B) and a nutrient (C) solution below a balloon either inflated (A) or deflated (B and C).

C, C_{max} were achieved at 2 h, when the perfusion was stopped.

Discussion

Absorption in jejunum and ileum

The data from Study I show that oxprenolol perfused directly in the intestine rapidly dis-

appears from the upper jejunum and middle ileum. As the stability of oxprenolol in intestinal fluids has been assessed by *in vitro* incubation (Vidon *et al.*, 1986), the disappearance of the drug from the intestinal lumen can be equated to absorption.

The lower fraction absorbed in the ileal segment (ratio of mean value ileum/jejunum = 0.76) might be indicative of a preferential oxprenolol absorption in the jejunum. However, the data recorded in Study I for ileum (% absorbed = 48) were not significantly different ($P = 0.60$) from those recorded in Study II for jejunum (52%) in other subjects, under identical intubation conditions. This suggests that, despite the differences observed in Study I, the absorption capacities of these two intestinal regions are not markedly different.

Approximately 30 cm of upper jejunum or middle ileum were able to absorb 50–60% of oxprenolol perfused as a saline solution. Assuming comparable absorption capacities within and below the test segment, the perfused drug would be completely absorbed in around 1 m of intestine.

It has been already demonstrated by a colonoscopic technique (Antonin *et al.*, 1985) that oxprenolol is absorbed from the colon. These results, combined to those obtained previously (Vidon *et al.*, 1986) and presently in Study I, indicate that oxprenolol given as an Oros system will be absorbed all along the small and large intestines.

The direct introduction of oxprenolol at two different levels of the GI tract resulted in similar plasma concentration-time profiles of the unchanged drug and its conjugates. The intra-subject variability of AUC values was small and negligible in comparison with the variability between subjects. The latter reflects the inter-individual differences of the first-pass metabolism of oxprenolol (Mason & Winer, 1976).

The AUC values of free oxprenolol were slightly higher after ileal perfusion, indicating that the total amount of drug available for absorption in the intestine after introduction in the upper jejunum could have been lower. The similar increase in AUC for conjugated oxprenolol (+12%, vs +17% for free), showed that the availability difference could not be related to differences in metabolism after ileal perfusion.

The plasma profiles of oxprenolol were representative of the absorption along and below the test segment. By contrast, the absorption rates were related to a segment of jejunum or ileum of around 30 cm. This can explain the difficulty of relating plasma concentrations to intestinal absorption rates. For one subject, identical absorption rates in jejunum and ileum resulted in AUC values differing by 30%. For another subject, a slight difference in AUC (+13% for ileum) was associated to a large difference in absorption rates (−50%).

Influence of nutrients and digestive secretions

As already observed for metoprolol (Evard *et al.*, 1985), the presence of endogenous secretions in the intestinal segment did not modify the rate of disappearance of oxprenolol from the lumen.

When the nutrient solution was perfused (C), oxprenolol was almost completely absorbed. Nutrients were, directly or indirectly, responsible for the increase of the rate of drug disappearance. As a segment about 30 cm long was able to

absorb 96% of the perfusate, oxprenolol would be completely absorbed in 60 cm of jejunum.

The same influence of nutrients on intestinal disappearance rate of metoprolol has been already reported (Evard *et al.*, 1985).

Oxprenolol disappearance from the lumen is probably not linked to net water movements since similar drug absorption rates were observed with either water secretion or absorption.

The systemic availability of oxprenolol was unaffected by nutrients. Oxprenolol was absorbed more rapidly and on a shorter length of jejunum in the presence of nutrients. This resulted in a faster appearance of the drug in plasma (initial phase in curve C, Figure 2). The differences in AUC were small and negligible in comparison with the variability between subjects.

Similar observations have been already reported after oral administration of various oxprenolol formulations with food. The ratios of the mean AUCs fed/fasting were found to be 1.025 and 1.17 for conventional tablets (Dawes *et al.*, 1979; John & Smith, 1985), 0.91 for Oros systems and 1.0 for slow-release tablets (John & Smith, 1985). In comparison, this ratio (C/B; Table 2) was 0.97 for the jejunal perfusion. Different delivery kinetics (as it is the case with an osmotically controlled delivery system, a standard or a slow-release tablet or an intestinal perfusion) of oxprenolol in the presence of food do not result in different availabilities of this drug.

In conclusion, the present findings, together with those previously reported (Vidon *et al.*, 1986; Antonin *et al.*, 1985) demonstrated that there is no selective site of absorption of oxprenolol between pylorus and colon. The rate of oxprenolol absorption from jejunum is unaffected by endogenous secretions, but it markedly increased in the presence of nutrients. However, the alteration in the absorption rate has no effect on the systemic availability of this drug.

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