Br. J. clin. Pharmac. (1985), **19**, 97S–105S

Investigation of drug absorption from the gastrointestinal tract of man. I. Metoprolol in the stomach, duodenum and jejunum

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1 Gastrointestinal (GI) absorption of the β-adrenoceptor blocker metoprolol was investigated in five healthy subjects by means of an intubation method, employing a triple-lumen tube introduced into the intestine, and a twin-lumen tube in the stomach. Metoprolol was introduced into the stomach with a homogenized meal containing a non-absorbable marker, [^{14}C]-PEG 4000, and another marker, PEG 4000, was perfused continuously into the duodenum just below the pylorus. Samples of GI contents were collected at regular intervals over 4 h in the stomach and at two different levels in the upper small intestine.

2 Metoprolol was not absorbed from the stomach. Approximately 60% of the amount of drug emptied from the stomach was absorbed from the duodenum; about 50% of that leaving the duodenum was absorbed from the first part of the jejunum. The delivery process was the rate-limiting factor of metoprolol absorption in these segments of the gut.

3 Plasma concentrations reflected drug loss from the lumen and were higher in subjects exhibiting faster gastric emptying and higher absorption rates in the duodenum and jejunum.

4 The intubation technique appeared to be a suitable method for investigating drug absorption from the GI tract in man.

Keywords drug absorption metoprolol stomach duodenum jejunum

Introduction

The gastrointestinal (GI) tract plays a fundamental role in the absorption of drugs. However, this important parameter in drug kinetics is usually evaluated by indirect methods based on a mathematical treatment of plasma concentration data. These methods require knowledge of the pharmacokinetic model from previous intravenous studies, and they may be disturbed by any process occurring between the GI tract and the systemic circulation. Direct methods have rarely been applied to the measurement of drug absorption in the gut (Sandle *et al.*, 1981; Sladen & Dawson, 1975).

We approached this problem by applying to drugs a technique previously described for investigating digestive physiology after ingestion of meals (Bernier & Lebert, 1971; Malagelada *et al.*, 1976; Meerof *et al.*, 1975). It is based on the following principle: after intubation of the stomach and intestine, gastric and duodenojejunal functions are evaluated by measuring the dilution of two aqueous non-absorbable markers, one present in a meal and the other simultaneously perfused into the duodenum. Gastric emptying, absorption from the duodenum and from the first part of the jejunum, as well as gastric, biliary and pancreatic secretion rates can be determined using this approach.

In the present study this intubation method has been used to study the GI absorption of the β-adrenoceptor antagonist, metoprolol, given with a homogenized meal to healthy volunteers.

Methods

Test meal and markers

The test meal consisted of 90 g steak, 50 g bread, 15 g olive oil, 80 g pear sherbet and 190 ml water. Its total caloric value was 450 calories, distributed as 40% carbohydrates, 40% fats and 20% proteins. The meal was homogenized for 30 s in a blender, with 30 μCi of [^{14}C]-labelled polyethylene glycol 4000 ([^{14}C]-PEG 4000) and 100 mg of metoprolol tartrate. After blending, the volume, osmolality and pH were 400 ml, 553 mosmol/kg and 5.6, respectively. Unlabelled PEG 4000 (20 g/l) in normal saline solution was perfused into the duodenum as a duodenal recovery marker at a flow rate of 2 ml/min.

Procedure

Five healthy subjects (aged 21–28 years) with normal gastrointestinal and cardiovascular function participated in the study. They received a detailed explanation of the study and gave their informed consent.

They were advised not to take any drug during the 8 days preceding the study and none besides metoprolol during its duration. They were also requested not to smoke during the perfusion period.

The evening before the study, a triple-lumen duodenal tube was positioned fluoroscopically with a perfusion site at the ampulla of Vater (B), a duodenal aspiration site at the angle of Treitz (C) and a jejunal aspiration site (D) 30 cm distal to this point. A double-lumen gastric sump-tube was positioned with its tip in the antrum (A). A schematic representation of the tubes in the GI tract is shown in Figure 1. The volunteers remained in a sitting position for the 4 h period of the study.

After 1 h of basal gastric aspiration, the homogenized meal was introduced into the stomach over 8 min by means of the gastric tube. Thereafter, gastric and duodeno-jejunal contents were sampled every 20 min for 4 h. The gastric contents were aspirated with a syringe. Duodenal and jejunal samples were aspirated using an intermittent pressure of −40 mm Hg. Negative pressures of 120 mm Hg have previously been shown not to alter motility of the antro-duodenal segment (Rees *et al.*, 1979) and should not have influenced gastric emptying in the present study. After 4 h, the gastric contents were aspirated and the stomach rinsed with 200 ml of normal saline containing 5 g of PEG 4000.

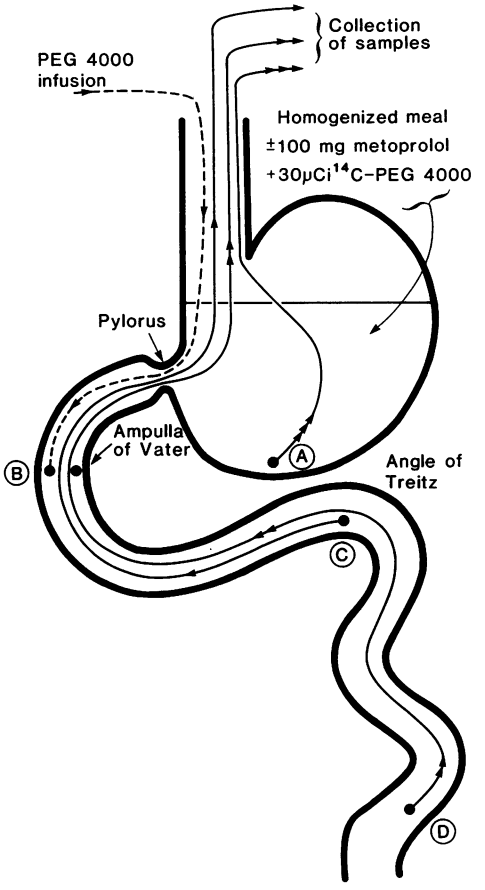

Figure 1 Diagram of the siting of the tubes within the GI tract. Distance from B to C = 20 cm; distance from C to D = 30 cm.

Blood samples were collected into heparinized tubes at fixed intervals over 4 h. Plasma was separated by centrifugation. All samples were stored at −20°C until analysed.

Analytical methods

The concentrations of PEG 4000 were measured by a turbidimetric method (Hyden, 1955), and those of [^{14}C]-PEG 4000 by liquid scintillation counting (Wingate *et al.*, 1972).

The concentrations of metoprolol in gastric, duodenal and jejunal fluids were determined by high-performance liquid chromatography. The

drug was extracted into hexane and chromatographed on a reversed-phase column (RP 8–10 μm) with u.v. detection at 225 nm. The mean recovery was 99 ± 6.2% in the range of 11–220 μg/ml of gastric fluid, 101 ± 6% in the range of 5.5–55 μg/ml of duodenal and jejunal fluids. The limit of quantitation was 1 μg/ml for each of the three fluids; the coefficient of variation was approximately 10% for six replicate values. The concentrations of metoprolol in plasma (expressed as metoprolol tartrate) were determined by a gas chromatography method (Sioufi *et al.*, 1983). The limit of quantitation of this assay was 10 ng/ml.

Data treatment

Data analysis was based on the theory developed to investigate gastric emptying of liquid and solid-liquid meals in man (Malagelada *et al.*, 1976; Meerof *et al.*, 1975).

The principal step in the analysis was the measurement of duodenal flow rate from the dilution of PEG 4000 between the ampulla (B) and the angle of Treitz (C). Duodenal [^{14}C]-PEG output (equivalent to pyloric [^{14}C]-PEG output) was estimated from the duodenal [^{14}C]-PEG concentration multiplied by duodenal flow rate. Pyloric flow rate was obtained by dividing duodenal [^{14}C]-PEG output by the concentration of [^{14}C]-PEG in the stomach, measured over the same time interval. Pyloric metoprolol output was taken as the product of drug concentration in the stomach and pyloric flow rate.

Duodenal metoprolol output was calculated from the duodenal concentration of the drug and duodenal flow rate. Duodenal absorption was estimated from the difference between pyloric and duodenal output of the drug. Jejunal flow rate was calculated similarly from jejunal dilution of PEG. Jejunal absorption was obtained from the difference between duodenal and jejunal output of metoprolol.

Gastric absorption was estimated from the difference between the amount given with the meal and that leaving the stomach (amount passing the pylorus + amount removed with gastric sampling). It was also assessed by the ratio of [^{14}C]-PEG to metoprolol in every gastric sample, since [^{14}C]-PEG is non-absorbable. Total [^{14}C]-PEG recovery was measured by summing the amount in gastric samples, the amount in the final gastric aspiration, and the calculated [^{14}C]-PEG output at the pylorus. The mean value (± s.e. mean) for the five subjects was 92.4 ± 2.2%.

Results

Gastric absorption of metoprolol (Table 1)

The actual amount of metoprolol given with the meal ranged from 93.2 to 95.5 mg. The difference between this amount and that lost from

Table 1 Gastric absorption of metoprolol. The amount absorbed over 4 h is the difference betweeen the amount given with the meal and the sum of that remaining in and having left the stomach

	Subjects					
	1	*2*	*3*	*4*	*5*	*Mean ± s.e. mean*
Amount given with the meal (mg)	94.3	94.7	93.2	95.5	95.3	94.6 ± 0.4
Amount in gastric samples (4 h) (mg)	10.4	11.2	8.3	8.5	18.3	11.3 ± 1.8
Amount delivered at pylorus (4 h) (mg)	63.5	70.2	71.1	88.2	42.7	67.3 ± 7.3
Amount left in the stomach after 4 h (mg)	11.7	0.3	0	0	17.3	5.9 ± 3.6
Amount absorbed in stomach (mg)	8.7	13	13.2	0	17	10.4 ± 2.9
% of given dose	9.2	13.7	14.2	0	17.8	11.0 ± 3.0

the stomach by gastric emptying and sampling over 4 h corresponded to 11% of the total administered. As this percentage is within the range of experimental error (the same calculation gave 7.6% for [^{14}C]-PEG), absorption of the drug from the stomach was clearly negligible. The constancy of metoprolol to [^{14}C]-PEG ratio in each gastric sample over 4 h postprandially also reflects the lack of gastric absorption of the drug.

Gastric emptying of metoprolol

Gastric emptying of metoprolol varied considerably between subjects (Figure 2). For two subjects (3 and 4), the amounts of drug emptied within a period of 2 h corresponded to 63 and 72% of the total amount that could have been emptied, i.e. the amount introduced in the stomach minus the amounts sampled during 2 h. The values for subjects 1, 2 and 5 during the same interval were 36, 40 and 19% respectively. In subjects 1 and 5, who exhibited lower emptying rates, 14 and 22%, respectively, of the total amount introduced less the amount sampled was still present in the stomach at 4 h after drug ingestion. In the other subjects, no drug was recovered at this time.

Duodenal absorption of metoprolol

The individual cumulative amounts of metoprolol absorbed from the duodenum are displayed in Figure 3. These absorption curves closely reflected the gastric emptying profiles (Figure 2), suggesting that the emptying rate regulates duodenal absorption. The relationship between duodenal absorption and gastric delivery was linear for metoprolol (Figure 4). The slope of approximately 0.6 for the regression line indicates that roughly 60% of the drug emptied from the stomach was absorbed from the duodenum. Individual absorptive capacities for this segment ranged from 53 to 71% of that delivered at the pylorus over 4 h (Table 2).

Jejunal absorption of metoprolol

The cumulative amounts of metoprolol absorbed in the jejunum were low (Figure 5) because the greater part of the amount delivered at the pylorus had already been absorbed in the duodenum. The inter-individual differences in jejunal profiles were of similar magnitude to those observed in the duodenum. Almost complete delivery of metoprolol was achieved, 2 h after drug intake for subjects 3 and 4, and 3.5 h after intake for subject 2. For subjects 1 and 5, the drug was still being delivered to the jejunum 4 h after ingestion with the meal.

A linear relationship between delivery and absorption rates was also obtained for the jejunum (Figure 6). The drug delivery rate at the angle of Treitz thus appears to be the main determinant of absorption distally to this point, resulting in a three to six fold variation between subjects in the present study. Approximately 50% of the drug available at the angle of Treitz was absorbed in the first part of the jejunum (Table 2).

Overall the duodenal and jejunal test segments in the proximal intestine were able to absorb a mean of 81% of the total amount of metoprolol emptied from the stomach (Table 2, Figure 7).

Plasma concentrations of metoprolol (Figure 8)

The highest plasma concentrations were recorded for subjects 3 and 4, who exhibited rapid gastric emptying as well as high absorption rates in the duodenum and jejunum. For these two subjects, a maximum concentration of approximately 75 ng/ml was achieved between 1 and 2 h after drug intake with the meal, whereas the concentrations recorded for subjects 1, 2 and 5 did not change significantly after an initial increase during the first hour after drug ingestion (Figure 8).

As judged from the AUC values, low bioavailability was associated with low rates of delivery and absorption. Inter-individual differences in bioavailability, however, were not related to the total amount of metoprolol absorbed in the upper small intestine (duodenum + jejunum) over 4 h (Table 3).

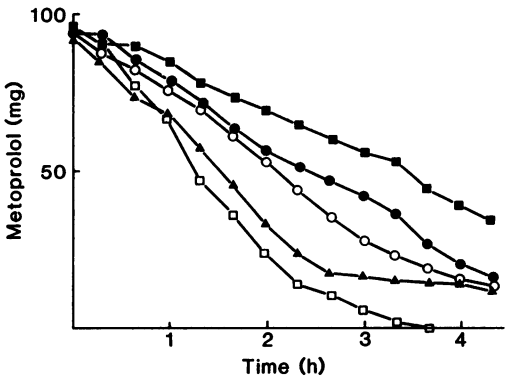

Figure 2 Gastric emptying of metoprolol taken with a meal. Each point represents the amount of metoprolol remaining in the stomach at intervals of 20 min over 4 h. (Subjects: 1, ●; 2, ○; 3, ▲; 4, □; 5, ■).

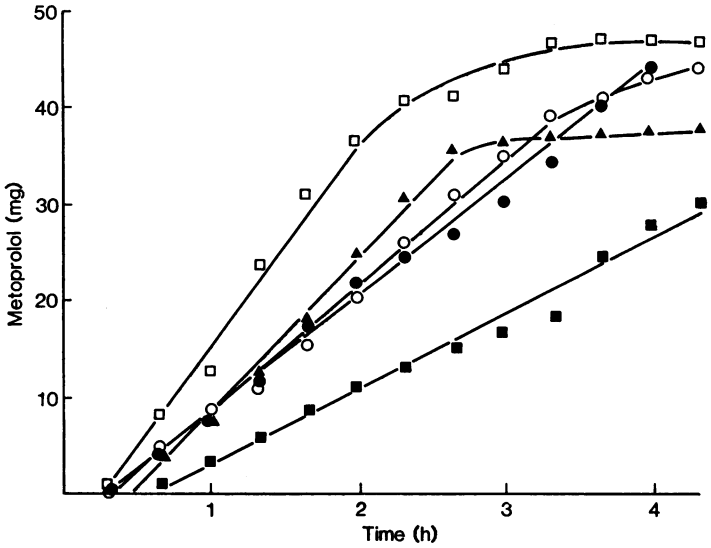

Figure 3 Duodenal absorption of metoprolol taken with a meal. Each point represents the cumulative amount of metoprolol absorbed at intervals of 20 min over 4 h. (Subjects: 1, ●; 2, ○; 3, ▲; 4, □; 5, ■).

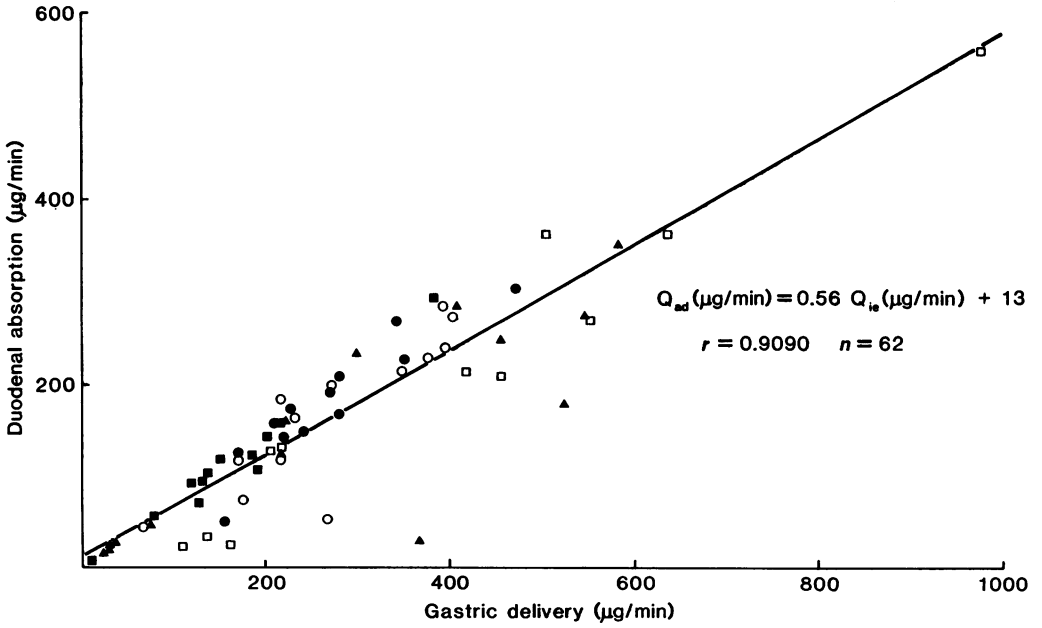

Figure 4 Duodenal absorption of metoprolol. Relationship between gastric delivery and duodenal absorption rates. Q_{ad} is the duodenal absorption rate, Q_{ie} the delivery rate from the stomach. (Subjects: 1, ●; 2, ○; 3, ▲; 4, □; 5, ■).

Table 2 Duodenal, jejunal and duodeno-jejunal absorption capacities of metoprolol taken with a meal: amounts of drug absorbed as a percentage of that delivered at the pylorus and at the angle of Treitz during a 4 h period.

Subject	*1*	*2*	*3*	*4*	*5*	*Mean ± s.e. mean*
Duodenum	69	62	53	53	71	62 ± 3.8
Jejunum	38	41	49	44	81	51 ± 7.8
Duodenum + jejunum	81.5	78	78	74	96	81.5 ± 3.8

Discussion

This paper describes the direct evaluation of drug absorption in the upper GI tract of man using an intubation method previously developed for investigating digestive physiology after the ingestion of food. It is based on the measurement of gastric emptying of a marker contained in a meal by dilution of a second non-absorbable marker perfused in the duodenum. This approach also allows gastric and pancreato-biliary secretions to be measured simultaneously (integrated response) after natural solid-liquid, mixed or liquid test meals.

For the measurement of drug absorption in the GI tract to be valid, the perfusion technique must not disturb digestive physiology. Although intraduodenal perfusion of fluid may stimulate intestinal neurohormonal responses, transpyloric tubes do not influence gastric emptying and secretion or gastrinaemia (Longstreth *et al.*, 1975). Reflux of duodenal contents into the stomach (another potential source of error) has been shown to be negligible, if it exists at all (Go *et al.*, 1970; Rees *et al.*, 1979). Gastric and intestinal samples are probably more representative of luminal content when liquid rather than solid-liquid meals are given, since sampling difficulties may occur in the case of solid contents. Therefore the measurement of postprandial drug absorption by intestinal intubation is likely to be more accurate when the meal is given in a homogenized or simple liquid form.

The measurement of intraluminal flow rates by dilution of a duodenal marker implies steady-state conditions and a constant gastric emptying rate. Such conditions are unlikely to exist during the first few hours after food intake resulting in an error of approximately 15% in the calculated duodenal flow rate over the whole period of meal evacuation (MacGregor *et al.*, 1977; Malagelada *et al.*, 1979; Meerof *et al.*, 1975).

Our data show that metoprolol taken with a liquid meal is not absorbed in the stomach but is extensively absorbed in the first part of the upper small intestine. Thus, the bioavailability of metoprolol from the GI tract depends on the gastric emptying rate, which varies considerably between subjects. Moreover, postprandial absorption of metoprolol will be influenced by other factors capable of modifying the gastric emptying pattern: caloric content and osmolality of the meal, vagotomy, gastric surgery, gastroparesis, etc. (Hunt & Stubbs, 1975). Under our experimental conditions, metoprolol has been shown not to influence gastric emptying (Jobin *et al.*, 1985), but other drugs which modify gastric evacuation may alter its intestinal absorption.

The amounts of drug absorbed appear to be directly related to the amounts delivered to the intestine by the stomach. This is reflected by the high plasma concentrations recorded in subjects who exhibited rapid gastric emptying and high intestinal absorption rates. The greater part (80%) of the total amount of metoprolol delivered at the pylorus is absorbed in the

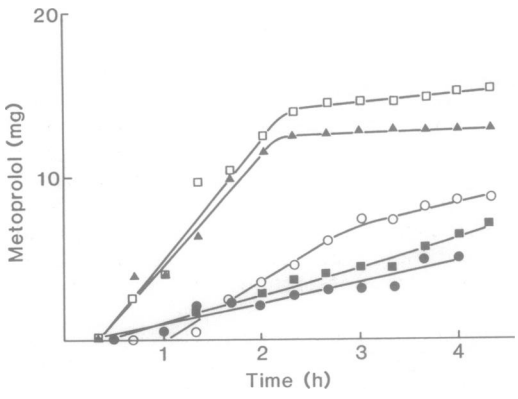

Figure 5 Jejunal absorption of metoprolol taken with a meal. Each point represents the cumulative amounts of metoprolol absorbed at intervals of 20 min over 4 h. (Subjects: 1, ●; 2, ○; 3, ▲; 4, □; 5, ■).

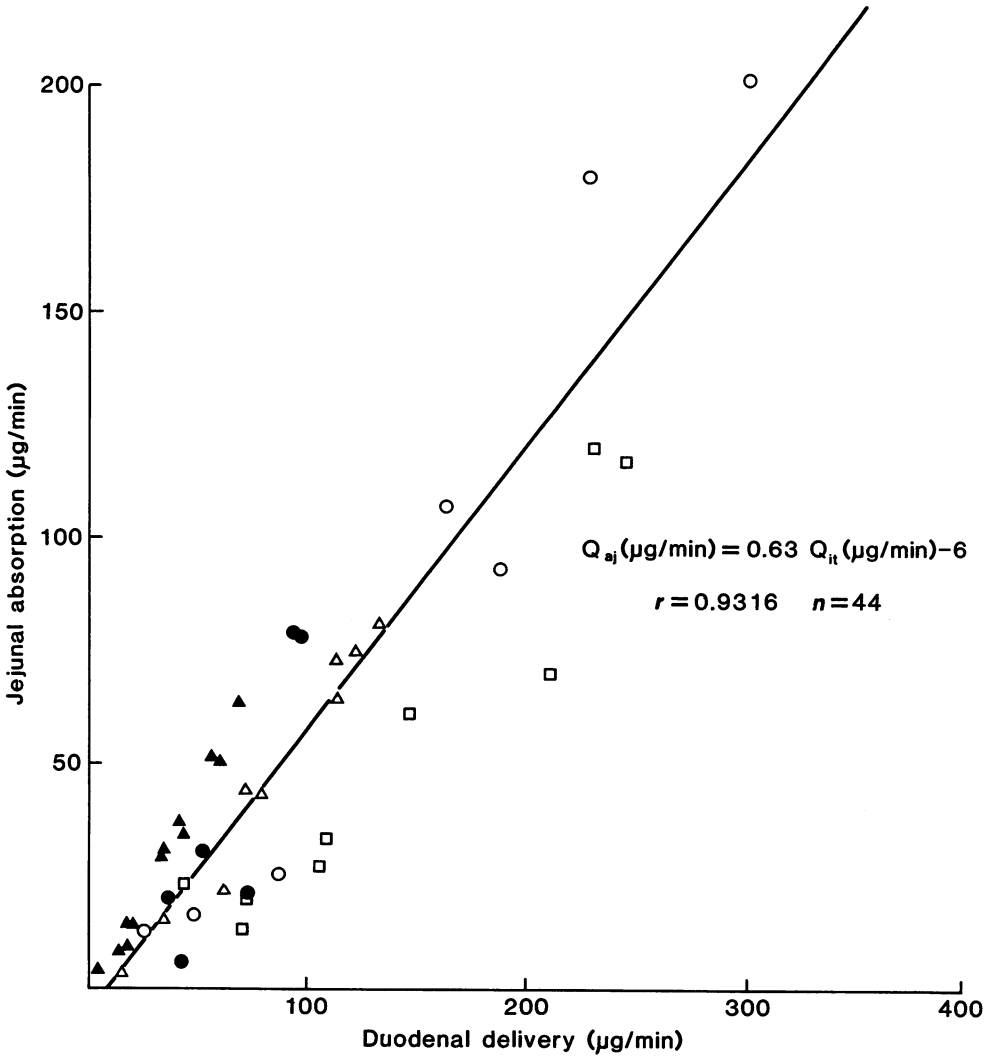

Figure 6 Jejunal absorption of metoprolol. Relationship between duodenal delivery and jejunal absorption rates. Q_{aj} is the jejunal absorption rate and Q_{it} the duodenal delivery rate at the angle of Treitz. (Subjects: 1, ●; 2, ○; 3, ▲; 4, □; 5, ■).

duodeno-jejunum. If the amounts absorbed per cm of intestine are expressed as a percentage of the amount delivered, the absorption rate constants estimated for the duodenum (0.032/cm) and jejunum (0.024/cm) were clearly similar. This may be due to regular arrival of the drug in the proximal GI tract combined with a high absorptive capacity of these GI segments for metoprolol.

In this study the digestive absorption of metoprolol was measured after the drug had been taken with a homogenized liquid meal, which is obviously not the normal form in which food is taken. However, it has been shown (Malagelada *et al.*, 1979) that the emptying of the aqueous phase of the gastric contents is similar after ingestion of a liquid or a solid-liquid meal. Only the solid and lipid phases of the gastric contents are emptied more slowly after ingestion of a meal in its natural solid-liquid form. Therefore our data are probably valid for drug absorption after ordinary meals.

The plasma concentrations observed at roughly 2 h after drug administration with the meal appeared to be related to the amounts of metoprolol entering the duodenum or the jejunum and to the amounts absorbed over 2 h from both intestinal segments. For subjects 3 and 4, who exhibited high plasma concentrations, these amounts were, on average, two to four

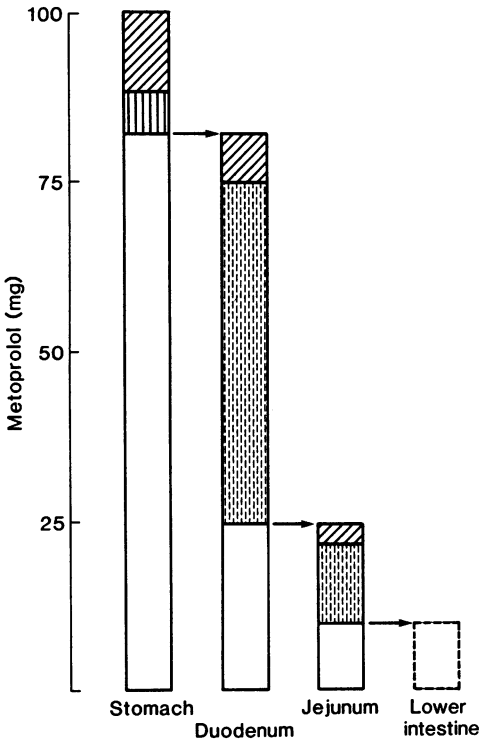

Figure 7 Schematic representation of the fate of metoprolol in the upper part of the GI tract after administration of 100 mg with a homogenized meal (mean values $n = 5$).
▨ sampled; ▥ remaining after 4 h; ▦ absorbed; □ delivered.

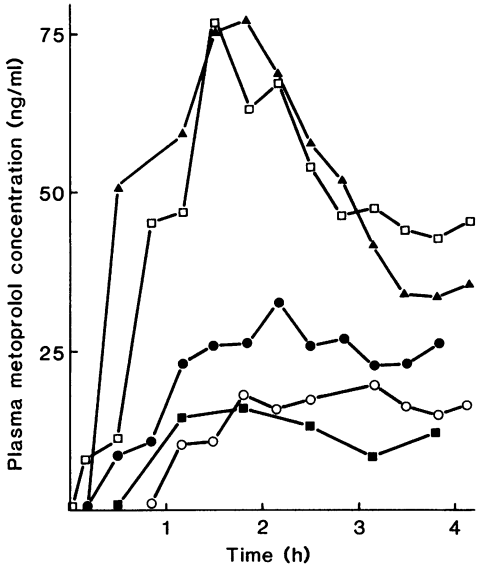

Figure 8 Plasma concentrations of metoprolol after administration of a single 93.2–95.5 mg dose incorporated into a homogenized meal. (Subjects: 1, ●; 2, ○; 3, ▲; 4, □; 5, ■).

which resulted in delayed intestinal absorption. times higher than those recorded for the other subjects. The curves of subjects 2 and 5 showed delayed appearance of metoprolol in plasma; this was related to a slow gastric emptying rate

These findings suggest that slow absorption could result in enhancement of the first-pass effect, increasing the biotransformation of metoprolol and reducing the concentration of the parent drug in the systemic circulation.

The results obtained in the present study demonstrate the validity of the intubation technique with a test meal to investigate the absorption pattern of a drug in the stomach, duodenum and jejunum.

The authors wish to thank Professor P. Massias (Hôpital de Bicêtre, France) who supervised the selection of subjects.

Table 3 AUC values and amounts of metoprolol absorbed in duodenum and jejunum over 4 h after ingestion of the meal.

Subject	*1*	*2*	*3*	*4*	*5*
AUC (ng ml h^{-1})	79*	50*	208*	193*	49+
Amount of metoprolol absorbed in duodenum + jejunum (mg)	45.9	50.4	50.4	60.5	37.0
AUC per mg absorbed	1.7	1.0	4.1	3.2	1.3

*AUC over 250 min
+AUC over 290 min

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