*Br. J. clin. Pharmac* (1985), **19**, 107S–112S

# Investigation of drug absorption from the gastrointestinal tract of man. II. Metoprolol in the jejunum and ileum

N. VIDON[1], D. EVARD[1], J. GODBILLON[2], M. RONGIER[1], M. DUVAL[2], J. P. SCHOELLER[3], J. J. BERNIER[1] & J. HIRTZ[2]

[1]INSERM U 54, Hôpital Saint-Lazare, 107 rue du Faubourg Saint-Denis, 75010 Paris, France, [2]Ciba-Geigy Biopharmaceutical Research Centre, and [3]Ciba-Geigy Medical Department, BP 308, 92506 Rueil Malmaison Cedex, France

**1** Absorption of metoprolol in jejunum and ileum was investigated in eight healthy subjects using an intestinal perfusion technique below an occlusive balloon. An isotonic saline solution, with or without metoprolol, was perfused at a flow rate of 10 ml/min, either at the angle of Treitz or in the middle part of the ileum. The absorption in a 30 cm intestinal segment was evaluated at metoprolol concentrations of 20, 40 and 60 mg/l.

**2** Metoprolol did not affect gut motility.

**3** Metoprolol was similarly absorbed in the jejunum and ileum. The absorption rates appeared to be linearly related to the perfusion rates and to the mean concentration in the segment, indicating a first-order kinetic process.

**4** The absorption rate of metoprolol perfused in the jejunum in a saline solution appeared to be lower than that observed after gastric administration of the drug incorporated in a meal.

**5** The findings in this and other studies in this series indicate that metoprolol is similarly absorbed throughout the small intestine.

**Keywords** drug absorption metoprolol ileum jejunum

## Introduction

The intubation method has been used by Jobin *et al.* (1985) to investigate the gastrointestinal absorption of metoprolol in man after ingestion with a meal. The results demonstrated that the drug is not absorbed in the stomach, and that its absorption is similar in the duodenum and in the upper part of jejunum. The purpose of the present study was to evaluate metoprolol absorption in the jejunum and ileum after drug delivery in a saline solution directly into the small bowel.

## Methods

Eight healthy male subjects (aged 24–29 years), with no evidence or history of gastrointestinal or cardiovascular disease, were selected. They gave informed consent to participate after receiving a full explanation of the protocol. They were advised to take no drug during the 8 days preceding the study and none other than metoprolol during the 3 days of intubation. When necessary, nitrazepam was administered at night.

*General procedure*

Intestinal flow rates, and metoprolol absorption, were measured in the jejunum or ileum while perfusing a saline solution containing: NaCl 130 mmol, KCl 5 mmol, mannitol 30 mmol, polyethylene glycol 4000 (PEG 4000, a non-absorbable marker) 5 g, and metoprolol at concentrations of 20, 40 or 60 mg/l. The perfusion rate was 10 ml/min and the total duration of administration 5–7 h.

In the jejunum, the solution was perfused at three different concentrations in four subjects, and at two concentrations in the other four subjects. In the ileum, the solution was perfused at three different concentrations in three subjects, and at two concentrations in another two subjects.

*Study design*

The study consisted of two parts each of which was carried out over three consecutive days. In the afternoon of the first day, the subjects were intubated with a four-lumen tube which also incorporated an occlusive balloon (Phillips & Summerskill, 1966). This balloon, once inflated, avoided contamination by endogenous secretions, and reflux of the perfusate above the infusion point. Immediately above the balloon, a tube (No. 1 in Figure 1) allowed continuous aspiration of the luminal content. The infusion tube opening (No. 3) was immediately below the balloon. The intestinal content was recovered by siphonage via tube No. 4, the orifice of which was 30 cm distal to the infusion point. Thus the test segment was 30 cm long. Tube No. 2 was used to inflate the balloon. A bag containing 1 ml of mercury was attached 20 cm below the sampling site.

In the morning of the second day the perfusion point, checked radiologically, was positioned just beyond the angle of Treitz. At the beginning of the infusion the balloon was inflated with 50 ml of air. Its occluding effect was checked with bromosulfophthalein (BSP), introduced above the balloon, with sampling below the balloon. In addition, the non-appearance of metoprolol above the balloon during perfusion of the solution was verified.

On the third day the same procedure was followed with drug being perfused either in the jejunum at different concentration, or in the middle part of the ileum at the same concentration. The subjects fasted for 12 h before each part of the study and remained fasting during the whole perfusion period. Two protocols were followed:

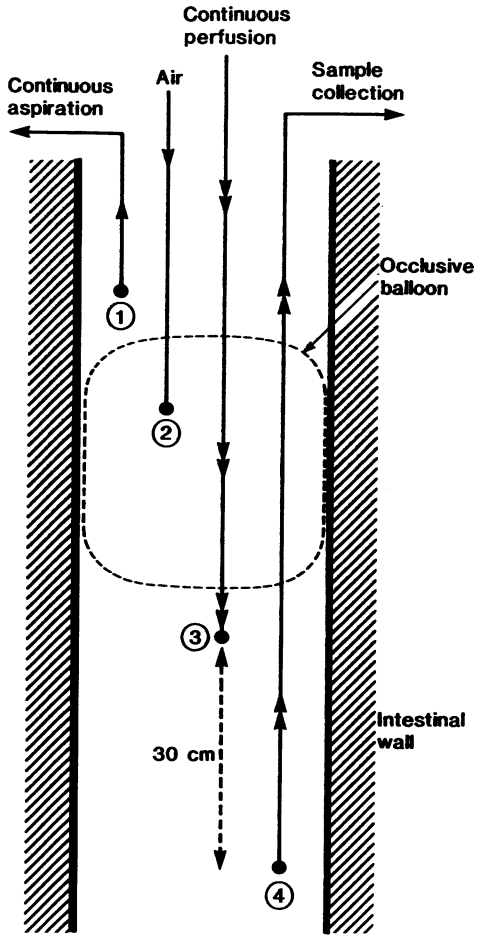


**Figure 1** Schematic representation of the tubes in the intestine.

*Protocol I: evaluation of the absorption rate* This protocol was designed to measure the absorption rate of metoprolol, and consisted of: (a) an 80 min equilibration period to obtain a hydrodynamic steady state—this was monitored by measuring PEG concentrations in three samples collected after 60, 70 and 80 min while the control solution (saline solution without metoprolol) was being perfused; (b) a 60 min equilibration period to obtain an absorptive steady-state of metoprolol—this was monitored by collecting three 10 min samples while a test solution containing metoprolol was perfused at a flow rate of 10 ml/min; and (c) and 80 min rinsing period, during which eight 10 min samples were collected while perfusing the control solution into the intestinal segment to eliminate metoprolol from the lumen. The last two steps in the procedure were then repeated with the different metoprolol concentrations.

*Protocol II: evaluation of the stability of the absorption process* This protocol was designed to monitor the absorption rate of metoprolol over 160–200 min, and consisted of: (a) a 50 min hydrodynamic equilibration period, during the last part of which three 10 min samples were collected while perfusing the control solution; and (b) a 30 min absorptive equilibration period, followed by collection of 16 or 21 samples at 10 min intervals while a test solution (40 or 60 mg/l) was being perfused; the amount of metoprolol administered on each occasion never exceeded 100 mg/day. This part of the study was performed only in the jejunum, and a single metoprolol concentration was studied each day.

*Calculations and statistical analysis*

The amount of metoprolol absorbed in the intestinal segment per unit of time, $Q_a$, was calculated as the difference between the amount entering and that recovered at the sampling site. It is given by:

$$Q_a = MET_T \times F_T - MET_S \times F_S,$$

where $MET_T$ and $MET_S$ are, respectively, the concentrations of metoprolol in the perfusate (T), and in the sample (S) collected at the aspiration site; $F_T$ and $F_S$ represent the flow rates at the site of perfusion and aspiration, respectively.

$F_S$ was calculated from the concentrations of the non-absorbable marker, PEG, in the perfused solution ($PEG_T$) and sample ($PEG_S$). Since equal amounts of this marker entered and left the intestinal segment,

$$PEG_T \times F_T = PEG_S \times F_S$$

and the absorption rate of metoprolol is given by:

$$Q_a = F_T \left(MET_T - MET_S \times \frac{PEG_T}{PEG_S}\right)$$

The data were compared by *t*-test for unpaired samples, and by correlation analysis.

*Analytical methods*

The concentrations of metoprolol in the perfusate and intestinal fluid were measured by high-performance liquid chromatography (Jobin *et al.*, 1985), determinations being done in duplicate using 200 µl samples. The limit of quantitation was 1 µg/ml. PEG 4000 concentrations were determined by turbidimetry (Hyden, 1955).

## Results

The absorption rates of metoprolol, $Q_a$, measured in a 30-cm segment of jejunum and ileum, were similar (Table 1) and appeared to be linearly related to the perfusion rate, $Q_i$ (Figure 2). Increasing the amount of drug available in the intestine per unit time produced a corresponding increase in the amount absorbed over the same time interval. The relationship between $Q_a$ in µg/min/30 cm, and $Q_i$ in µg/min in the jejunum was:

$$Q_a = 0.16\ Q_i + 6.9\ (r = 0.66, n = 20; P < 0.01),$$

and in the ileum was:

$$Q_a = 0.22\ Q_i - 3.6\ (r = 0.77, n = 13; P < 0.01)$$

The calculated relationship for the combined jejunum and ileum segments was:

$$Q_a = 0.18\ Q_i + 3.1\ (r = 0.69; P < 0.001).$$

There was no significant difference (*t*-test: $P > 0.05$) between the absorption rates of metoprolol, expressed as percentages of the perfusion rate, when solutions containing 20, 40 or 60 mg/l were perfused either in jejunum or in ileum (Table 1). However, the s.e.mean values

**Table 1** Mean (± s.e. mean) absorption rates ($Q_a$) of metoprolol (expressed as µg $min^{-1}$ 30 $cm^{-1}$ and as a percentage of perfusion rates $Q_i$) in jejunum and ileum during continuous perfusion of solutions containing 20, 40 or 60 mg/l, at a flow rate of 10 ml/min.

| *Intestinal segment* | *Metoprolol perfused (µg/ml)* | *Metoprolol absorbed (µg $min^{-1}$ 30 $cm^{-1}$)* | *Percentage $Q_i$* |
|---|---|---|---|
| Jejunum | 20 ($n$ = 6)** | 39 ± 5 | 18.6 ± 2.0 |
| | 40 ($n$ = 6) | 67.5 ± 13 | 17.1 ± 3.7 |
| | 60 ($n$ = 8) | 103 ± 14 | 17.2 ± 2.3 |
| Ileum | 20 ($n$ = 5) | 46 ± 6 | 22.9 ± 2.7 |
| | 40 ($n$ = 3) | 66 (54 – 88)* | 16.7 (13.5 – 20.5)* |
| | 60 ($n$ = 5) | 130 ± 24 | 22.4 ± 4.1 |

*Range of values

**$n$ = number of subjects given this solution

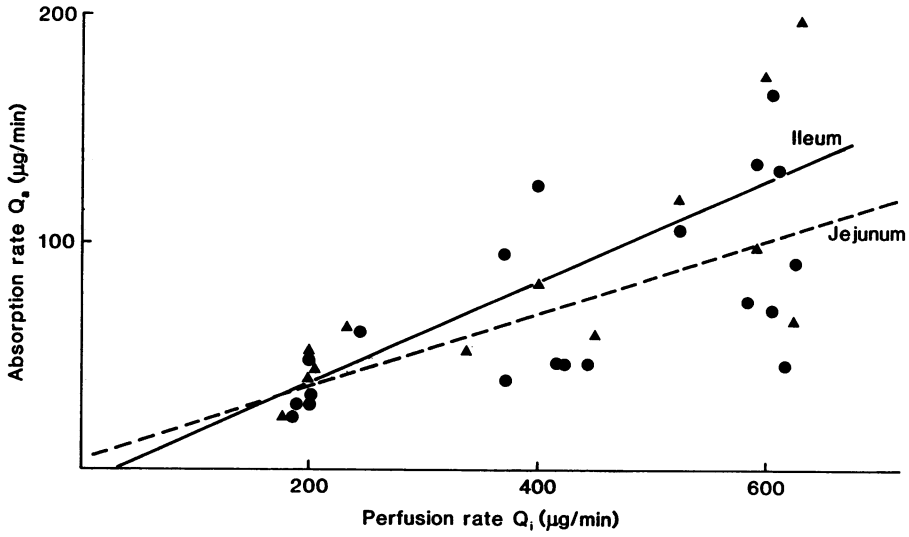


**Figure 2** Relationship between the perfusion and absorption rates of metoprolol in jejunum and ileum. Individual values in the jejunum (●, $n = 20$) and ileum (▲, $n = 13$) in a total of eight subjects (see Table 1).

indicate greater variability at higher drug concentrations, although differences between individuals were generally large.

The perfusion flow rate was identical for the three metoprolol concentrations. As a concentration gradient exists along the intestinal segment, a mean concentration, $C_m = (MET_T + MET_S)/2$, was calculated to examine its relationship with the absorption rate. For the combined segments the latter, expressed as µg $min^{-1}$ 30 $cm^{-1}$, appeared to be linearly related to this mean concentration in µg/ml, the equation being:

$$Q_a = 1.66\ C_m + 14.2\ (r = 0.58;\ P < 0.001).$$

The possible change of the absorption rate with time, as well as its intra-individual variability, was evaluated in two subjects according to protocol II. The results for one subject are given in Figure 3, and show that the intraluminal concentration of metoprolol, measured at the sampling site during perfusion of the drug at a concentration of 40 and 60 mg/l, remained constant over 2.5 and 3.5 h, respectively. Similarly, there was no significant change in the rate of absorption during continuous perfusion, and the mean values were 47 and 82 µg/min for $Q_i$ values of 368 and 584 µg/min, respectively. Not surprisingly, the ratios of $Q_a$ to $Q_i$ were similar, and were 0.13 and 0.14 at metoprolol concentrations of 40 and 60 mg/l, respectively.

After stopping the perfusion of metoprolol but continuing with the control solution, the disappearance of the drug from the lumen followed first-order kinetics (Figure 4).

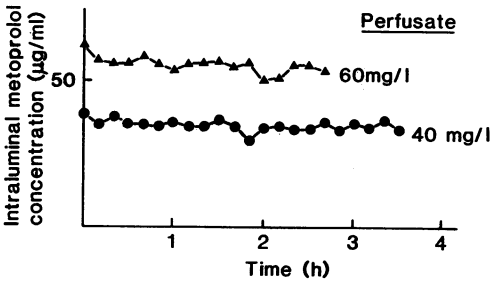


**Figure 3** Concentrations of metoprolol at the sampling site in the jejunum during 2.5 and 3.5 h of continuous perfusion of a solution containing 60 mg/l (▲—▲) and 40 mg/l (●—●), respectively, to one individual.

## Discussion

The data obtained in the present study show, for the first time in man, that metoprolol perfused directly into the intestine is absorbed in the jejunum and ileum. The similarity of the absorption rates in both segments indicates that there is no preferential site of metoprolol absorption in the small intestine.

The linear relationship between absorption rate and mean concentration is indicative of first-order kinetics, and of passive diffusion across the intestinal mucosa. Such a mechanism is generally accepted for the absorption of drugs in the small intestine (Prescott, 1974).

When the perfusion of metoprolol was stopped, the control solution displaced metoprolol from the 30-cm intestinal segment. Thus

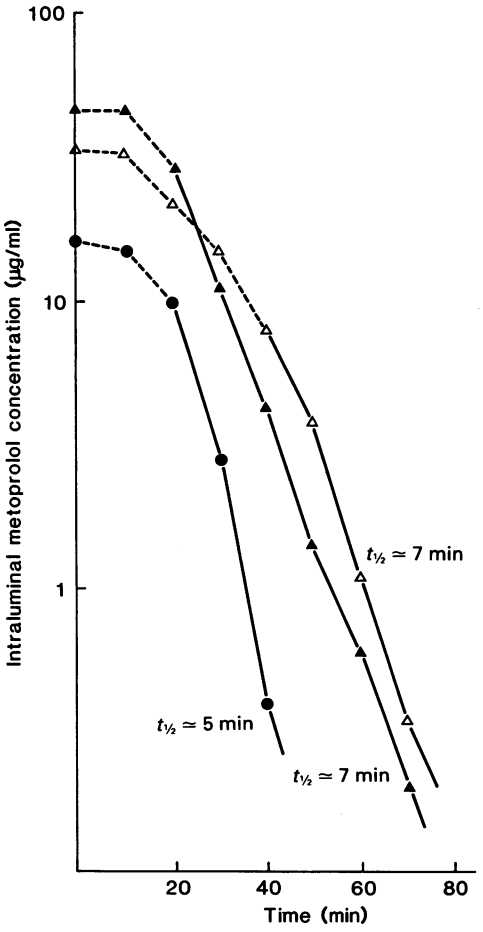


**Figure 4** Disappearance of metoprolol from the lumen after perfusion of solutions containing 20 (●), 40 (○) or 60 (▲) mg/l when a marker solution without metoprolol was perfused at the same flow rate. Individual data points represent mean concentrations in jejunum and ileum in a total of eight subjects (see Table 1). The estimated half-lives at the three concentrations were 5, 7 and 7 min, respectively.

the rate of disappearance of the drug can provide a measure of the flow, or transit time, of solution through the small intestine (Figure 4). The half-life of intraluminal disappearance of the drug was found to be independent of the metoprolol concentration in the perfused solution. In addition, the value estimated for metoprolol (5–7 min) was similar to that for bromosulfophthalein, an inactive compound (Matuchansky *et al.*, 1969). This suggests that metoprolol (at the concentrations used) did not modify the mechanical conditions in the small bowel, and therefore did not affect intestinal motility. Morris & Turnberg (1981) have shown that another β-adrenoceptor antagonist, propranolol, given intravenously, had no significant motor effect on the human small intestine.

In another study in the present series (Jobin *et al.*, 1985) the absorption rate of metoprolol in the jejunum was found to be linearly related to the delivery rate at the angle of Treitz when the drug was administered in the stomach with a meal, the proportionality factor being 0.63. The present study, in which metoprolol was perfused in the jejunum in a saline solution under fasting conditions, gave a proportionality factor of 0.16. This suggests that administering metoprolol with a meal could directly or indirectly increase its absorption rate in the upper jejunum by a factor of approximately 4. Food has previously been shown to enhance the bioavailability of metoprolol (Melander *et al.*, 1977). The direct effect of food and digestive secretions on metoprolol absorption rate has also been evaluated in another study (Evard *et al.*, 1985).

In the present study, the drug was perfused in a saline solution directly into the small bowel, and the results showed that approximately 18% of the perfused amount was absorbed in the 30 cm test segment. Extrapolation of this finding to the total small bowel length (about 180 cm between the angle of Treitz and the caecum) suggests that about 70% of the perfused drug would be absorbed in the small intestine, and the remaining 30% would reach the colon. Thus, when an individual takes metoprolol with water, under fasting conditions, a significant amount may reach the colon. The colonic absorption of metoprolol is the subject of a separate study in this series (Godbillon *et al.*, 1985).

In conclusion, the present findings, together with those reported by Jobin *et al.* (1985), demonstrate that metoprolol is absorbed at a similar rate throughout the small intestine.

The authors wish to thank Professor P. Massias (Hôpital de Bicêtre, France), who was responsible for subject selection.

## References

Evard, D., Vidon, N., Godbillon, J., Bovet, M., Duval, M., Schoeller, J. P., Bernier, J. J. & Hirtz, J. (1985). Investigation of drug absorption from the gastrointestinal tract of man. IV. Influence of food and digestive secretion on metoprolol jejunal absorption. *Br. J. clin. Pharmac.*, **19**, 119S–125S.

Godbillon, J., Evard, D., Vidon, N., Duval, M., Schoeller, J. P., Bernier, J. J. & Hirtz, J. (1985). Investigation of drug absorption from the gastrointestinal tract of man. III. Metoprolol in the colon. *Br. J. clin. Pharmac.*, **19**, 113S–118S.

Hyden, S. A. (1955). A turbidimetric method for the determination of high polyethylene glycols in biological materials. *Ann. Roy. Agric. Coll. Sweden,* **22**, 139–145.

Jobin, G., Cortot, A., Godbillon, J., Duval, M., Schoeller, J. P., Hirtz, J. & Bernier, J. J. (1985). Investigation of drug absorption from the gastrointestinal tract of man. I. Metoprolol in the stomach, duodenum and jejunum. *Br. J. clin. Pharmac.*, **19**, 97S–105S.

Matuchansky, C., Sterin, D., Rambaud, J. C. & Bernier, J. J. (1969). Temps de transit et calibre de l'intestin grêle chez l'homme: Mesure par la courbe de dilution d'un colorant au cours d'une perfusion intestinale de solutés isotoniques de NaCl et KCl. *Biol. Gastroenterol.*, **58**, 45–58.

Melander, A., Danielson, K., Schersten, B. & Wahlin, E. (1977). Enhancement of the bioavailability of propranolol and metoprolol by food. *Clin. Pharmac. Ther.*, **22**, 108–122.

Morris, A. I. & Turnberg, L. A. (1981). Influence of isoproterenol and propranolol on human intestinal transport *in vivo*. *Gastroenterology,* **81**, 1076–1079.

Phillips, S. F. & Summerskill, W. H. J. (1966). Occlusion of the jejunum for intestinal perfusion in man. *Mayo Clin. Proc.*, **41**, 224–231.

Prescott, L. F. (1974). Gastrointestinal absorption of drugs. *Med. Clin. North Am.*, **58**, 907–916.