REGIONAL ABSORPTION OF METOPROLOL IN HUMANS DETERMINED BY A NEW METHOD SUITABLE FOR STUDIES IN THE WHOLE GASTRO-INTESTINAL (GI) TRACT

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INTRODUCTION

Knowledge of regional absorption properties of a drug in the GI tract is imperative for rational design of an oral extended release (ER) formulation. The presently available techniques, such as capsules with radiotelemetric control of release (1), intubations (2) and pharmacoscintigraphy (3), have provided very useful results. However, an optimal method is characterized by a) access to the whole GI tract and precise targeting to desired regions b) possibility of repeat or continuous delivery of one or more substances within one study session c) no discomfort to the subject. None of the present techniques fulfills all requirements. A new method has therefore been developed with the aim to meet the above defined goals (4). The aim of the present study was to further evaluate the new method in an investigation of the absorption properties in man of metoprolol, a $\beta_1$-selective adrenoceptor antagonist mainly used for the treatment of hypertension, in upper jejunum, distal ileum and proximal colon.

MATERIAL AND METHODS

Description of method
The method uses a small-bore, smooth, polyethylene tube with a firm radio-opaque body at the end. The tube was first introduced through the subject's nose into the pharynx from where it was retrieved through the mouth. The firm body was then mounted on the tube and swallowed. After having left the stomach, the firm body was moved by peristalsis through the intestine. The length of swallowed tube was recorded from scale marks on the tube, and the desired position of the tube was verified by fluoroscopy. Administration of drug in solution was performed through a syringe connected to the outside part of the tube. After completion of desired administrations, the tube was cut at the mouth of the subject and the firm body and the tube left the gut through the anus.

Study design
In the morning after overnight fasting, metoprolol tartrate solution 25 mg was administered as bolus doses in eight healthy subjects at three different locations in the GI tract. The study was performed in two periods with one week of wash-out in between. In the first period, the subjects arrived in the laboratory at 22 p.m. for introduction of the tube. Drug administration to the distal ileum was performed in the following morning. In the second period, the subjects arrived in the laboratory at 7 am. Introduction of the tube and drug administration in proximal jejunum was performed during that same morning and delivery to the proximal colon in the morning the following day. Plasma was frequently sampled for assay of metoprolol concentrations (5) during 8 hours after each administration. Standardized meals were served 2, 5 and 8 hours after drug intake. Area under the curve of plasma concentration vs. time (AUC), maximum plasma concentration (Cmax), time to Cmax (tmax), and terminal elimination rate constant (ke) were calculated for metoprolol. The AUC for the colon administration was corrected for overlap from previous administration by use of ke. Statistical differences were analyzed by ANOVA and 95 % confidence intervals were constructed for the differences.

RESULTS AND DISCUSSION

No adverse events were reported. All subjects included completed both study periods. Drug administrations were successful at all three locations in all subjects, except in one case of intended colon administration where the tube did not reach the colon in due time. No administration was therefore performed and the experiment was terminated.
The mean plasma concentrations and bioavailability variables of metoprolol in the three different regions are given in Figure 1 and Table 1, respectively. The mean plasma profiles of metoprolol were similar and no statistically significant differences were obtained. This shows that metoprolol is taken up to the same extent and rate in the whole intestine in accordance with findings in an other study (6).

Table 1
Mean bioavailability variables and 95% confidence intervals (CI) for difference between ileum and jejunum (il/jej) and between colon and jejunum (col/jej)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean</th>
<th>95% CI</th>
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<tbody>
<tr>
<td>Cmax (nmol/L)</td>
<td>jej 90, il 130, col 110</td>
<td>0.9;2.2^1, 0.7;1.9^1</td>
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<tr>
<td>tmax (h)</td>
<td>jej 1.1, il 0.8, col 0.8</td>
<td>-0.9;0.3, -0.9;0.3</td>
</tr>
<tr>
<td>AUC (h•nmol/L)</td>
<td>jej 386, il 380, col 405</td>
<td>0.7;1.4^1, 0.8;1.5^1</td>
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In conclusion, the results from the present study merit further use of the new method. Furthermore, the favourable absorption prerequisites for use of metoprolol ER delivery systems with drug release also in distal parts of the GI tract have been verified.

REFERENCES