Uptake in the Human Small Intestine of a Quaternary Anticholinergic Compound (Acabel)

B. BEERMANN, K. HELLSTRÖM and A. ROSÉN

Department of Medicine and Clinical Pharmacology Laboratory, Serafimerlasarettet, Stockholm, Sweden

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Summary. The anticholinergic compound Acabel (the benzilic acid ester of N,N-dimethyl-2-hydroxy-methylpiperidinium-methylsulphate), tritium labelled in the piperidine molecule, was administered to 6 healthy volunteers. Its absorption was measured by comparing the radioactivity in gastrointestinal aspirates with that of an unabsorbed marker. The main uptake of Acabel was localized in the upper part of the small intestine, and amounted to 10—20% of the given dose. — Studies in vitro showed that \(^3\)H-Acabel can be metabolized in the small intestine. However, in vivo there was no evidence of its decomposition while the test solution was passing through the proximal part of the digestive tract.

Key-words: Anticholinergics, gastrointestinal agents, intestinal absorption, parasympatholytics.

In spite of the extensive medical use of anticholinergic drugs very little is known about their gastrointestinal absorption in man. The available data indicate that the degree of absorption differs greatly between the various drugs of this kind, e.g. although atropine is almost completely taken up (Beermann, Hellström & Rosén 1971), less than 10% of butylscopolamine is absorbed (Hellström, Rosén & Söderlund 1970).

The benzilic acid ester of N,N-dimethyl-2-hydroxy-methylpiperidinium-methylsulphate (Acabel), which has been shown to have anticholinergic properties (Osterloh et al. 1966), has been recommended for medical use. The aim of the present investigation was to study the gastrointestinal uptake of this compound in man.

Material and Methods

Seven male bus drivers, 38—53 years old, volunteered for this investigation (Table 1). In each of them an intraintestinal double-lumen tube was inserted through the nose and allowed to pass to the desired level before the start of the experiment. The position of the tube was controlled by X-ray. \(^3\)H-Acabel (100 mg, 50 \(\mu\)Ci) dissolved in 50 ml water, was administered orally in the morning to the subjects, who had fasted overnight. Polyethylene glycol (PEG, 5 g) was added to the test solution as an unabsorbable marker. Water (100 ml) was given each hour for 4 h. In one experiment, 2.5 mg (25 \(\mu\)Ci) Acabel was dissolved in 20 ml saline and injected intravenously.

Aspirates of gastric and intestinal content were collected at various time intervals. Cholecystokinin (37.5 I.U. units) was injected intravenously to obtain concentrated bile (Table 1). Samples of venous blood were drawn at 15, 30, 45 min, and at 1, 2, 4, 7, 10 and 24 h after the start of the experiment. Urine and faeces were collected continuously for 6 days.

Table 1. Experimental Protocol

<table>
<thead>
<tr>
<th>Experiment No.</th>
<th>Subject</th>
<th>Administration</th>
<th>Collection of faeces urine (days)</th>
<th>Gastrointestinal aspiration</th>
<th>Injection of cholecystokinin. Time after administration of label (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>GD</td>
<td>oral</td>
<td>6 6</td>
<td>80 and 110</td>
<td>4, 7 and 10</td>
</tr>
<tr>
<td>2</td>
<td>HD</td>
<td>oral</td>
<td>6 6</td>
<td>80 and 110</td>
<td>4, 7 and 10</td>
</tr>
<tr>
<td>3</td>
<td>BL</td>
<td>oral</td>
<td>6 6</td>
<td>80 and 200</td>
<td>4, 7, 10 and 24</td>
</tr>
<tr>
<td>4</td>
<td>ST</td>
<td>oral</td>
<td>6 6</td>
<td>80 and 200</td>
<td>4, 7, 10 and 24</td>
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<tr>
<td>5</td>
<td>KH</td>
<td>oral</td>
<td>— —</td>
<td>50</td>
<td>—</td>
</tr>
<tr>
<td>6</td>
<td>AR</td>
<td>oral</td>
<td>— —</td>
<td>50</td>
<td>—</td>
</tr>
<tr>
<td>7</td>
<td>KA</td>
<td>intravenous</td>
<td>6 6</td>
<td>50 and 80</td>
<td>1, 2 1/2, 4 and 6 (\alpha)</td>
</tr>
</tbody>
</table>

\(\alpha\) Cholecystokinin was also injected 1 h prior to administration of label.

Experimental procedure

Acabel (9.6 \(\mu\)Ci/mg), randomly labelled with tritium in the piperidine molecule, was obtained from Chemie Grünenthal, GmbH, Stolberg/Rhld. The labelled compound was purified by chromatography on a Sephadex column, and its radiopurity was checked by high voltage electrophoresis (Hellström et al. 1970). More
than 98% of the radioactivity accumulated in the same area as inactive Acabel.

Polyethylene glycol (m.w. 4000, Kebo Co., Stockholm, Sweden) was measured according to Hydén's method (1955), and bilirubin, by that of Nosslin (1960). The method of Engstedt et al. (1967) was used for the determination of bilirubin turnover. The cholecystokinin-pancreozymin preparation was obtained from the G.I.H. Research group, Department of Chemistry, Karolinska Institutet, Stockholm, Sweden.

Radioactivity determination

Samples of blood plasma were dried to a powder at 30°C, and a modified combustion technique according to Schöniger (1955) was used on aliquots of it. The condensed water was dissolved in scintillation liquid (Bray 1960) and its radioactivity assessed in a liquid scintillation spectrometer (Packard Tri-Carb, model 3003). Faeces were homogenized in water, and aliquots were lyophilized and subjected to combustion as described above. Aliquots of urine (1 ml), and of gastric and intestinal aspirates (0.1 ml) were mixed directly with the scintillation liquid, and their radioactivity measured as above.

High voltage paper electrophoresis

Samples (20 µl) of intestinal content containing more than 500 cpm per 20 µl were applied directly to chromatographic paper (Whatman No. 1). High voltage electrophoresis (12 kv, 50 mA) was performed in a solution of concentrated formic and acetic acids and water (2 : 3 : 15 v/v). The paper strips were cut into several segments, each of which was assessed for radioactivity by combustion. The segment with non-metabolized Acabel was identified by comparison with the reference substance run in parallel, and visualized with an iodosyl platinate spray.

Results

Oral administration

The ratio between the radioactivity per mg PEG of aspirated specimens of the gastric content and that of the test solution (A/T ratios) ranged between 0.89 and 1.02, and averaged 0.93 (n = 6), and 0.95 (n = 8) in the two subjects studied. In duodenal aspirates obtained during the first hour from two other subjects.