A comparison of Boots and GIH secretin as stimuli of pancreatic secretion in human subjects with or without chronic pancreatitis

L. V. GUTIERREZ AND J. H. BARON

From the Department of Surgery, Royal Postgraduate Medical School, London

SUMMARY The effects of single intravenous injections of 1 u/kg body weight Boots and 1 u/kg GIH secretin were compared in 10 male control subjects and five men with chronic pancreatitis. The duodenum was aspirated for the next hour in 4 × 10 minute and 1 × 20 minute fractions, and the volume, bicarbonate concentration, and tryptic activity were measured.

The duodenal juice volume and peak bicarbonate output in response to GIH secretin 1 u/kg iv were double the responses to Boots secretin 1 u/kg, but tryptic activity was significantly less. The coefficients of variation of these measurements were not appreciably improved by expression of the results in terms of body weight. Measurements of bicarbonate concentration or enzyme output in the submaximal pancreatic function tests using Boots secretin 1 u/kg were of some use as diagnostic discriminants between normal subjects and patients with chronic pancreatitis. However, these measurements were of little value with the test using a near-maximal stimulus of 1 u/kg GIH secretin. Measurement of peak bicarbonate output is probably the best diagnostic discriminant, and discrimination is not improved by expression of the results on a body weight basis.

The history of the bioassay of secretin in the dog, cat, and rat is complex and confusing (see Harper, 1967). Historically 1 Ivy dog unit and 1 Crick-Harper-Raper unit, and 1 (old) clinical unit are approximately equal and equivalent to 10 Love rat units and to 20 Hammarsten cat units.

Most clinical studies of pancreatic exocrine secretion have been done with the Boots preparation of secretin, which is assayed and expressed in the unit of Crick, Harper, and Raper (1949), and the conventional submaximal intravenous dose is 1 u/kg. Pure Jorpes and Mutt secretin is now also available commercially from the Gastrointestinal Hormone (GIH) Laboratory, Karolinska Institute, Stockholm, and its potency is expressed in clinical units. Jorpes and Mutt (1966) intended their clinical unit to be equal to the standard intravenous dose used in man by Hammarsten, Ågren, and Lagerlof (1937), the equivalent of 16 to 20 Hammarsten cat units/kg. However, because of instability and change in potency in the Swedish reference standard of secretin, the potency of the clinical unit of pure Jorpes and Mutt secretin was greater than the old clinical unit by a factor at first thought to be × 2 (Jorpes and Mutt, 1965), later × 3 to × 7 in the rat and × 4 to × 5 in the cat (Heatley, 1968), × 8 to × 9 in the dog (Stening, Vagne, and Grossman, 1968), and × 10 in the cat (Konturek, 1969).

We have therefore compared 1 so-called u/kg of Boots and GIH secretin in men with and without chronic pancreatitis, both to study the relative stimulatory effects of these two secretins in these doses, and also to compare the diagnostic discrimination between a dose of secretin (1 u/kg Boots) known to be submaximal (Bordalo, Teixeira, and Sakelarides, 1969) and a dose of secretin (1 u/kg GIH) which is known to be near maximal (Petersen, 1970).

Methods

SUBJECTS

Fifteen men were tested. Ten were free of pancreatic disease, four of whom were normal volunteers, and six were patients admitted for investigation of non-

1Correspondence: Dr J. H. Baron, Department of Surgery, R.P.M.S., Hammersmith Hospital, London W12 0HS.

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specific abdominal pain. The other five were patients with proven pancreatic disease, all of whom had clinical and biochemical evidence of chronic pancreatitis and two of whom had this diagnosis confirmed at laparotomy.

**TEST PROCEDURES**

Following an overnight fast the subject swallowed a double-lumen Dreiling tube which was positioned under fluoroscopic control with its tip in the fourth part of the duodenum in order to allow separate collection of gastric and duodenal contents. Simultaneous continuous aspiration with a suction pump was maintained through each tube. Two 10-minute basal samples were collected before stimulation. After a single intravenous injection of 1 u/kg body weight of secretin, samples were collected from the duodenum for one hour in fractions of 10, 10, 10, 10, and 20 minutes.

**ANALYTICAL METHODS**

Volume was measured to the nearest 0.5 ml. Bicarbonate concentration was determined by adding 0.1 N hydrochloric acid, boiling, and backtitrating with 0.1 N sodium hydroxide to pH 7 with an autoburet titrator. The peak bicarbonate output was expressed in milliequivalents per hour by multiplying by 3 the sum of the two highest consecutive 10-minute outputs. The trypsic activity of 0.1 ml duodenal juice was measured by a modification of the method of Haverback, Dyce, Gutentag, and Montgomery (1963) using a pH stat automatic recording titrator. The substrate was p-Tosyl-L arginine methyl ester (Tame, Sigma Chem Co) in 0.04M NaCl and 0.02M CaCl₂ adjusted to a pH 8.2 with HCl. Trypsin (British Drug Houses and SIGMA Chemical Company) standard was prepared for each set of determinations in a concentration of 100 mg/100 ml in 0.005N NaCl containing 0.005M CaCl₂. All determinations were made at 30°C. Tryptic activity was expressed in units; 1 unit = 1 ml per minute 0.01N NaOH required to maintain a constant pH of 8.2 at 30°C. The trypsic activity of each sample was measured and the output calculated for each sample as volume × trypsic activity. Tryptic activity was not measured in one of the control subjects and one of the patients with chronic pancreatitis.

**SECRETINS**

Boots secretin (batch no. 78) and GIH secretin (batch no. 16911) were purchased from their manufacturers.

**TIMING**

In seven subjects the two tests were done on different days. In the other eight the two tests were done on the same day, the other secretin being administered only after the volume of duodenal aspirate had returned to basal levels, in an attempt to minimize any effect of the first injection on the response to the second (Henriksen, 1966; Wormsley, 1969).

![Fig. 1](http://gut.bmj.com/) **Volume of duodenal aspirate (ml) in the 60 minutes after 1 u/kg secretin in 10 control subjects (○) and five patients with chronic pancreatitis (●). r = 0.91. y = 0.48x + 29.9**

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Unit</th>
<th>Boots Secretin</th>
<th>GIH Secretin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>CV</td>
</tr>
<tr>
<td>Volume ml in 60 min</td>
<td>143(87-169)</td>
<td>30</td>
<td>21</td>
</tr>
<tr>
<td>Volume ml in 60 min-kg</td>
<td>2.2(1.4-2.6)</td>
<td>0.4</td>
<td>18</td>
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<tr>
<td>Maximum bicarbonate concentration m-equiv/1</td>
<td>98(72-140)</td>
<td>23</td>
<td>24</td>
</tr>
<tr>
<td>Peak bicarbonate output m-equiv/h</td>
<td>15.8(10.5-22.3)</td>
<td>4.2</td>
<td>26</td>
</tr>
<tr>
<td></td>
<td>µequiv/h-kg</td>
<td>237(186-351)</td>
<td>62</td>
</tr>
<tr>
<td>Tryptic activity u/h</td>
<td>1040(270-1975)</td>
<td>682</td>
<td>65</td>
</tr>
<tr>
<td></td>
<td>u/kg</td>
<td>14.5(4.8-271)</td>
<td>8.6</td>
</tr>
</tbody>
</table>

Table I Measurements of duodenal juice in 10 male control subjects after intravenous injections of 1 u/kg Boots and GIH secretin with the ratios and significances of the differences between the responses to the two secretins
A comparison of Boots and GIH secretin as stimuli of pancreatic secretion

Fig. 2  Volume of duodenal aspirate (ml/kg) in the 60 minutes after 1 u/kg secretin. \( r = 0.88, y = 0.47x + 0.43 \).

Fig. 3  Maximum bicarbonate concentration (m-equiv/l). \( r = 0.56, y = 0.68x + 8.6 \).

Fig. 4  Peak bicarbonate output (m-equiv/h). \( r = 0.87, y = 0.56x - 0.01 \).

Fig. 5  Peak bicarbonate output (m-equiv/h/kg). \( r = 0.85, y = 0.47x + 14.7 \).

Fig. 6  Tryptic activity (u/h). \( r = 0.90, y = 0.64x + 108.1 \).

Fig. 7  Tryptic activity (u h\(^{-1}\) kg\(^{-1}\)). \( r = 0.86, y = 1.28x + 0.49 \).
Results

CONTROL SUBJECTS (TABLE I)
The pancreatic juice volume in one hour after the intravenous injection of GIH secretin, 1 u/kg, was nearly double the response to Boots secretin, 1 u/kg (Figs. 1-2). Maximum bicarbonate concentration was insignificantly higher (Fig. 3), and peak bicarbonate output correspondingly almost twice as great after GIH than after Boots secretion 1 u/kg (Figs. 4-5). The one-hour tryptic activity after GIH secretin was significantly lower than after Boots secretin (Figs. 6-7). The coefficients of variation of these measurements of pancreatic juice were not appreciably improved with either secretin by expression of the results in terms of body weight.

PATIENTS WITH CHRONIC PANCREATITIS (TABLE II): COMPARISON OF THE TWO SECRETINS
The volume response to GIH secretin was about one-fifth higher than to Boots secretin, but the maximum bicarbonate concentration was more than doubled, so that peak bicarbonate output after GIH secretin was about three and one-half times that after Boots secretin.

COMPARISON OF PATIENTS WITH PANCREATITIS WITH NORMAL SUBJECTS
The diagnostic discrimination for each measurement can be estimated (Fig. 1-7). Thus for juice volume in one hour the GIH secretin dose provided absolute discrimination between the two groups, whereas one of the patients with chronic pancreatitis fell within the normal range for the dose of Boots secretin (Figs. 1 and 2). On the other hand, for maximum bicarbonate concentration, the dose of Boots secretin provided absolute discrimination, whereas one of the patients with chronic pancreatitis fell within the normal range for the dose of GIH secretin (Fig. 3). Peak bicarbonate output in response to either secretin provided absolute discrimination (Figs. 4 and 5). The tryptic output after the dose of Boots secretin provided absolute discrimination, whereas after the dose of GIH secretin there was almost complete overlap between the two groups (Figs. 6 and 7). The diagnostic discrimination was not improved by expression of the results on a body-weight basis (Figs. 2 and 7).

Discussion

CONTROL DATA
The secretory responses to this dose of 1 u/kg Boots secretin are comparable to other reported data (such as Sun, 1963; Hansky, 1971) and less than the responses to a higher dose of 1-7 u/kg (Burton, Evans, Harper, Mowat, Oleesky, Scott, and Varley, 1960). The responses to 1 clinical u/kg GIH secretin are similar to those reported by Petersen (1970) and Konturek (1970). In the present study each patient received both secretins and it seems clear that 1 clinical u/kg GIH secretin elicited a secretory response from the normal human pancreas almost double that for 1 u/kg Boots secretin. No direct comparison of the potency of the two secretins can be made since dose-response curves were not done for each secretin in each subject. It is therefore not possible to estimate from these results what dose of Boots secretin would be needed in man to stimulate a pancreatic secretion equivalent to that evoked by 1 clinical u/kg GIH secretin, nor, conversely, what dose of GIH secretin is equivalent in man to 1 u/kg Boots secretin. The greater enzyme response to Boots secretin is presumably due to its considerable content of pancreozymnin, which may vary from batch to batch.

DIAGNOSTIC DISCRIMINATION
There is no general agreement whether the diagnostic discrimination between normal subjects and patients with chronic pancreatitis is best with a submaximal or with a maximal dose of secretin. Agren and Lagerlof (1936) injected 3 cat units/kg: "We have chosen this as our standard dose since there are reasons to

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Units</th>
<th>Boots Secretin</th>
<th>GIH Secretin</th>
<th>GIH/Boots</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (range)</td>
<td>SD</td>
<td>CV</td>
<td>SE</td>
</tr>
<tr>
<td>Volume</td>
<td>ml in 60 min</td>
<td>52 (21-117)</td>
<td>38</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td>ml in 60 min-kg</td>
<td>0.9 (0.5-1.9)</td>
<td>0.6</td>
<td>18</td>
</tr>
<tr>
<td>Maximum bicarbonate</td>
<td>concentration</td>
<td>m-equiv/l</td>
<td>31 (21-50)</td>
<td>11</td>
</tr>
<tr>
<td>Peak bicarbonate output</td>
<td>m-equiv/h</td>
<td>1.7 (0-6-3)</td>
<td>1.1</td>
<td>62</td>
</tr>
<tr>
<td>Tryptic activity</td>
<td>µ-equiv/h-kg</td>
<td>28 (10-46)</td>
<td>16</td>
<td>56</td>
</tr>
<tr>
<td>Tryptic activity</td>
<td>u/h</td>
<td>79 (17-175)</td>
<td>82</td>
<td>103</td>
</tr>
<tr>
<td></td>
<td>u/h-kg</td>
<td>1.4 (0-1.3-1)</td>
<td>1.3</td>
<td>91</td>
</tr>
</tbody>
</table>

Table II Measurements of duodenal juice in five men with chronic pancreatitis after intravenous injections of 1 u/kg Boots and GIH secretin with the ratios and significances of the differences between the responses to the two secretins.
believe that in pathological conditions . . . a subnormal function will be easier detected after submaximal stimulation. In the next 30 years there were many studies of the diagnostic discrimination of a submaximal dose of secretin (see Dreiling and Janowitz, 1962). With the demonstration of a maximum alkaline (bicarbonate) output of the dog pancreas, it was suggested that 'the measurement of maximum secretory capacity in man may allow more quantitative assessment of a secretory impairment' (Baron, Perrier, Janowitz, and Dreiling, 1963). There have been many human studies of this augmented secretin test with either Boots (Banwell, Northam, and Cooke, 1967; Pascal, Sannou, and Ribet, 1968; Bordalo et al, 1969; Hansky, 1971), Vitrum (Perrier, 1966; Hartley, Gambill, Engstrom, and Summerskill, 1966; Sarles, Prezlin, Souville, and Figarella, 1966; Lagerlöf, Schütz, and Holmer, 1967) or GIH secretin (Wormsley, 1968; Petersen, 1970).

There is now evidence (Baron, 1970) that a maximal gastric stimulus may allow greater diagnostic discrimination between normal gastric secretion and gastric hypersecretion (as in duodenal ulcer). The studies cited above suggest that an augmented secretin stimulus of maximum bicarbonate output may allow greater diagnostic discrimination than a submaximal stimulus between normal pancreatic secretion and pancreatic hyposecretion (as in pancreatitis). However, in none of these series were the same subjects given both a submaximal and a maximal stimulus.

The present results suggest that measurements of bicarbonate concentration or enzyme output which were of some use as diagnostic discriminants in the submaximal test using Boots 1 u/kg are of little value with the test using a near-maximal stimulus of 1 clinical u/kg GIH secretin. Measurement of maximal bicarbonate output is probably the best diagnostic discriminant between normal subjects and patients with pancreatitis (Wormsley, 1970) but the present series is too small to allow a definite preference for the near maximal stimulus.

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References


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