Effect of secretin on plasma motilin in man


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SUMMARY Graded doses of 0.1, 0.3, 0.9, and 2.7 clinical units/kg/h of pure synthetic secretin were infused over 60 minute periods in six healthy volunteers. Duodenal bicarbonate output and pH were recorded and plasma secretin and motilin levels were measured by radioimmunoassay. During the infusions plasma motilin fell in a dose dependent manner to a nadir of 35%. This fall was linearly correlated with pancreatic bicarbonate output, whereas a non-linear correlation was observed between plasma motilin and both plasma secretin level and duodenal pH. It is suggested that plasma motilin levels are decreased by secretin-induced pancreatic bicarbonate juice flow. This may be important for the control of motilin secretion initiated by duodenal acidification and the concomitant delay in gastric emptying.

Motilin, a recently discovered hormonal peptide from the small intestine (Brown et al., 1971), has been shown to increase lower oesophageal sphincter pressure and to delay gastric emptying in man (Ruppin et al., 1975; Rösch et al., 1976).

So far, no physiological regulation of motilin secretion has been ascertained. In the dog it has been reported that serum motilin levels are raised by strong duodenal alkalisation (Dryburgh and Brown, 1975). We have shown recently that, in man, motilin is released by duodenal acidification and after intraduodenal instillation of tris buffer (pH 10-2) motilin fell (Mitznegg et al., 1976). As, however, a duodenal pH of 10-2 is unlikely to be achieved under normal conditions, the significance of this finding is uncertain. The present study was designed to assess the effect on motilin release of secretin. This peptide initiates a physiological alkalisation of the duodenum by stimulating endogenous alkaline pancreatic juice flow (Jorpes and Mutt, 1961).

Methods

Six healthy volunteer men (aged 23-42 years) were studied after informed consent was obtained. Each subject underwent two tests, each after an overnight fast and separated by one week.

The first experiment was performed in order to establish the effect of graded infusions of secretin on pancreatic bicarbonate output and duodenal pH. The duodenum was drained via a modified Lagerlöf tube and duodenal fluid was collected throughout the experiment and corrected for recovery losses by continuous intraduodenal instillation of Ca⁶⁸ labelled vitamin B₁₂ as previously described (Tynpner et al., 1974). pH was measured conventionally and bicarbonate concentration was determined by titration in an atmosphere of N₂.

After a basal period of 20 minutes, synthetic secretin was infused via a cubital vein catheter into the upper caval vein. Graded doses of 0.1, 0.3, 0.9, and 2.7 clinical units (CU)/kg/h were administered for one hour each. The secretin was synthesised according to Wünsch et al. (1972). The material used had a biological activity of about 3-9 CU/μg, identical with the activity of pure natural secretin from G I H Research Unit, Karolinska Institute, Stockholm, Sweden (Lehnert et al., 1973). The reproducibility of the effect of secretin infusions on pancreatic juice flow in the same subjects has been established (Tynpner et al., 1974).

In the second experiment the effect of secretin infusions on plasma motilin was studied. The experiment was carried out exactly as described above except that no duodenal fluid was collected. Instead...
blood was withdrawn from an antecubital vein at 10 minute intervals during the basal period, at five minute intervals during the secretin infusions and thereafter at 10 minute intervals until 270 minutes. The samples (4.5 ml) were mixed with 1000 kallikrein inactivating units heparinised aprotinin (Trasylol) per ml, immediately centrifuged, and the plasma stored at —20°C until assay. The immunoassayable plasma secretin was determined as previously described (Bloom, 1975). The results were pooled to calculate the mean plateau levels of secretin for each dose of synthetic secretin infused.

Plasma motilin was measured by a highly specific and sensitive radioimmunoassay. Details of the assay are given elsewhere (Bloom et al., 1976). In brief, antibodies were raised to pure porcine motilin (gift of Professor J. C. Brown) and used at a final dilution of 1 in 320 000 to bind approximately 50% of the added motilin Iodine125. There was no cross-reactivity with other known gastrointestinal peptides and changes of 5 pmol/l plasma could be detected with 95% confidence. It has been shown previously that fasting human plasma motilin levels are fairly constant for each individual but vary considerably between subjects (Bloom et al., 1976). In order to put equal weight on each individual’s response, the plasma motilin levels in the present study were normalised. In the figures the motilin data are expressed as percentage (± SEM) of the individual mean baseline.

Results

In the present study the mean basal plasma motilin level (± SEM) was 62.2 ± 9.4 pmol/l. During the one-hour infusions of graded doses of 0.1, 0.3, 0.9, and 2.7 CU/kg/h secretin the mean motilin level fell to 50.9 ± 3.6 (p < 0.02), 44.0 ± 3.9 (p < 0.02), 26.0 ± 1.9 (p < 0.01), and 21.8 ± 1.8 (p < 0.002) pmol/l respectively and rose to 42.8 ± 11.1 (p < 0.2) pmol/l 25 minutes after termination of the infusions (p value from Student’s t test as compared with baseline level).

It can be seen from Fig. 1 that, whereas at lower infusion rates of secretin, some fluctuation of plasma motilin is observed, at higher doses (0.9, 2.7 CU/kg/h) a stable depression was achieved.

Figure 2 shows the semilogarithmic correlation between plasma secretin levels achieved during the infusions and the concomitant decrease of motilin. A typical S-shaped dose response curve was obtained. It demonstrates a maximal motilin decrease of about 65% corresponding to a plasma secretin level of 163 ± 0.8 pmol/l.

In Fig. 3 the plasma motilin levels are plotted against bicarbonate output and duodenal pH. Whereas bicarbonate output had a linear correlation with motilin inhibition over the range observed (r = 0.99 for mean values), pH had not. The initial fall in motilin was paralleled by a rise in pH though

Fig. 1 Plasma motilin in six volunteers during infusion of synthetic secretin. Motilin values are expressed as a percentage of each individual’s baseline (bars = SEM).
at higher levels of bicarbonate output this effect was no longer seen.
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