Comparison of the biological potency of a new synthetic preparation of secretin with that of natural porcine secretin in the dog


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SUMMARY The biological activity of the new synthetic secretin, Roche, on exocrine pancreatic secretion was determined in conscious dogs with chronic gastric and duodenal fistulae and compared with that of pure porcine secretin (GIH, Karolinska Institutet, Stockholm). The two secretin preparations were found to be equipotent as to pancreatic volume and bicarbonate response on a molar basis. It was concluded that the new synthetic secretin is useful for clinical and research purposes.

Although the amino acid sequence of secretin has been known since 1966 (Mutt and Jorpes, 1966) and the first synthesis was achieved in the same year (Bodansky et al., 1966), the peptide hormone is still not generally available for clinical use and is difficult to obtain for research purposes.

Recently a synthetic secretin preparation has been produced by F. Hoffmann-La Roche Co. Ltd., Basel, Switzerland, in close cooperation with Professor E. Wuensch. It was the purpose of this study to compare the biological activity of secretin Roche with that of natural porcine secretin (GIH secretin; Karolinska Institutet, Stockholm, Sweden) in conscious dogs.

Methods

Material
Roche secretin was kindly provided in the form of its pentacitrate salt by the Diagnostic Research Department of F. Hoffmann-La Roche Co. Ltd., Basel, Switzerland. This material was synthesised according to Wuensch (1972) and contained 72% of the dry, free base as determined by amino acid analysis. Pure natural porcine secretin (GIH secretin) was obtained in the form of its acetate salt as a generous gift from Dr V. Mutt, Karolinska Institutet, Stockholm, Sweden. The biological activity of the latter compound was specified as 4000 clinical units the (CU)/mg lyophilised secretin salt or 5000 CU/mg dry free base. As both preparations consist of salts of secretin with different acids, the weight percentages of the acid residues are different in both samples. To correct for this difference all dosages were calculated on the basis of the dry free secretin base.

Techniques
Four mongrel dogs, weighing 25, 26.5, 27.5, and 35.5 kg, were prepared with chronic duodenal fistulae by means of a modified Thomas cannula. The accessory pancreatic duct was ligated and a gastric cannula inserted into the stomach at the most dependent part. The dogs were allowed to recover from surgery for at least six weeks before the secretin studies were performed.

The animals were starved for 18 hours before the investigations but had free access to water. During the experiments they were kept standing supported by a sling harness.

Secretion studies
For the secretion studies a glass catheter connected by a short polyvinylchloride tube to a glass syringe was inserted into the main pancreatic duct through the duodenal cannula (dead space: 1 ml). The dependent plunger of the syringe exerted a slight negative pressure. Gastric juice was drained through the open gastric cannula. After the basal secretion had been collected for 15 minutes, exocrine pancreatic secretion was stimulated in each dog by four different doses of secretin GIH and Roche respectively in a randomised design by intravenous bolus injection. During the studies saline was infused by an electric pump at a constant rate of 50 ml/hour.

The doses were chosen to produce secretory responses remaining within the linear part of the dose-response curve when the pancreatic responses
were plotted against the logarithm of the doses. Thus 0.025 µg, 0.056 µg, 0.125 µg, and 0.280 µg of free secretin base GIH and Roche were administered per kg in a volume of 0.16 ml/kg body weight.

Pancreatic secretion was then collected in 15-minute periods until basal levels had been reached again. pH, volume, and bicarbonate output were determined, the latter according to the method of Lagerlöf (1942). The first 15-minute samples after secretin injection were used for statistical comparison.

Statistical analysis
The following test of significance was applied: for each dog and treatment, a parabolic dose-response-curve was assumed. The parabolas of the two treatments were compared with each other by the usual method of hypothesis testing in linear models (Searle, 1971). This test was performed for all four dogs simultaneously.

Results
The dose-response curves of the two secretin preparations were parallel and, in addition, nearly identical as can be judged from the data in Figs 1 and 2. The variances of the data were reduced when the parameters of pancreatic secretory response were corrected for body weight. Equimolar amounts of secretin Roche and GIH produced responses of volume and bicarbonate secretion which were not significantly different (p > 0.10). Therefore the relative potency of synthetic secretin base Roche compared to that of GIH secretin—that is, the ratio of doses producing equal responses—is not significantly different from 1.

Discussion
The results of this study indicate that the biological activity of secretin Roche as to pancreatic volume and bicarbonate secretion is equivalent to that of GIH secretin on an equimolar basis. According to the GIH Research Unit pure natural secretin has a potency of 5000 CU/mg dry free base. The same refers to secretin base Roche, as it has been found to be equipotent. When we took into account the different secretin base contents of the two preparations, the potency was 4.0 CU/µg GIH secretin and 3.6 CU/µg secretin Roche as such. These data are similar to those found in dogs treated with secretin Squibb (Vagne et al., 1968) showing an activity of 3.4 CU/µg
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Wuensch (Lehnert et al., 1972) with an activity of 3.52 CU/μg for volume secretion and 3.48 CU/μg for bicarbonate output. An approximately equivalent efficacy has also been observed for secretin Squibb in man—that is, 3.86 CU/μg (Farooq et al., 1974).

It is concluded from the present study that synthetic secretin Roche has the same potency as natural porcine secretin GIH. No side-effects were observed with either substance.

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References


