

## CLINICAL STUDY

## Plasma pancreatic polypeptide response to secretin

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### Abstract

**Objective:** Intravenously administered secretin stimulates pancreatic polypeptide (PP) release in patients with endocrine enteropancreatic tumors, but data in patients with nontumorous disorders are controversial. Therefore, we aimed to evaluate the plasma PP pattern after secretin administration in healthy subjects and in patients with gastroduodenal diseases investigated for recurrent ulcer disease and/or hypergastrinemia.

**Methods:** Synthetic secretin was given as an intravenous bolus (2 U/kg) in ten patients with Zollinger Ellison syndrome, ten with duodenal ulcer, ten with atrophic gastritis and ten healthy volunteers. Blood samples were taken before and at regular intervals for 30 min after secretin injection. Plasma PP and gastrin levels were measured by radioimmunoassay.

**Results:** Secretin promptly and significantly ( $P < 0.01$ ) increased PP plasma levels in all groups of subjects without any differences in peak values. There were no significant correlations between PP and gastrin plasma levels.

**Conclusions:** Secretin at pharmacological doses is a powerful stimulus for PP release.

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### Introduction

In patients with Zollinger Ellison syndrome (ZES) intravenously administered secretin induces a paradoxical rise in circulating gastrin levels (1). Moreover, in a series of 26 ZES patients Rigaud *et al.* (2) found that secretin infusion significantly increased plasma pancreatic polypeptide (PP) levels, and considered this response was also paradoxical since it was abolished by gastrinoma excision. Similar results have been reported in patients with PPomas (3). However, conflicting data have been found when secretin was administered to healthy subjects and to patients without evidence of endocrine enteropancreatic tumors. Indeed, preliminary studies showed that extractive secretin (Boot's secretin) was a potent releaser of PP in humans (4), but it was claimed that impurities of this crude extract could mediate the secretin effect (5), as slow infusions of purified secretin failed to consistently stimulate PP release in normal subjects and in duodenal ulcer patients (2). On the other hand, Glaser *et al.* (6) demonstrated that both purified and Boot's secretin, given as an i.v. bolus of 2 U/kg, induced significant PP responses in healthy subjects. Theoretically, the availability of synthetic secretin should allow clarification as to whether this peptide effectively stimulates PP release in humans, although in the two studies so far performed opposite results have emerged in normal

subjects (7, 8). Therefore, we aimed to evaluate the PP plasma pattern after a standard i.v. bolus (2 U/kg) of synthetic secretin in ZES patients and, for comparison, in healthy subjects and in patients investigated for recurrent ulcer disease or hypergastrinemia, who eventually were found to have *Helicobacter pylori*-associated duodenal ulcer or atrophic gastritis.

### Subjects and methods

The secretin test was performed in 10 patients with ZES (4 men and 6 women, aged 39–72 years, mean age 54), 10 patients with duodenal ulcer (5 men and 5 women, aged 38–72 years, mean age 55), 10 patients with atrophic gastritis (1 man and 9 women, aged 37–76 years, mean age 57) and 10 healthy volunteers (4 men and 6 women, aged 27–65 years, mean age 41). The study was approved by the local ethics committee.

Table 1 summarizes the main data on gastrin plasma levels in the four groups of subjects. ZES was diagnosed according to the established criteria (1); in all patients the secretin test resulted in a rise in gastrin levels greater than 200 ng/l. In four patients gastrinoma was a component of multiple endocrine neoplasia type I (MEN I) syndrome. All duodenal ulcer patients had evidence of *Helicobacter pylori* infection and showed normal fasting gastrin levels that did not change after

**Table 1** Plasma gastrin and PP responses to an i.v. bolus of secretin (2 U/kg) in healthy subjects and in patients with duodenal ulcer, ZES and atrophic gastritis. Data are means (S.E.M.), with the exception of gastrin data in patients with ZES and atrophic gastritis which are median and range.

Subjects	No. of cases	Gastrin (ng/l)		PP (pmol/l)	
		Basal	Peak/nadir	Basal	Peak
Controls	10	59 (6.0)	68 (8.3)	19 (1.9)	71 (12.4)*
Duodenal ulcer	10	66 (5.6)	78 (8.8)	23 (3.9)	102 (21.9)*
ZES	10	392† (133–27720)	1112* (349–36670)	32 (7.3)	107 (14.6)*
Atrophic gastritis	10	664† (215–1670)	376* (151–1090)	30 (6.1)	103 (21.8)*

\*  $P < 0.01$  vs basal (Wilcoxon test); †  $P < 0.01$  vs controls (Mann-Whitney test).

secretin administration. Patients with histologically proven atrophic gastritis had elevated fasting gastrin levels that decreased after secretin administration.

Secretin (Sekretolin, Hoechst, Frankfurt, Germany) 2 U/kg body weight was given i.v. over 1 min at time 0. All tests were started between 0900 and 1000 h after an overnight fast and one hour of bed rest. Blood was taken from a forearm venous cannula kept patent by slow saline infusion. Samples were collected in ice-chilled polypropylene tubes containing EDTA (1 mg/ml) and aprotinin (500 KIU/ml) 30 min and immediately before the secretin injection and at 2, 5, 10, 15, and 30 min after the secretin injection. Plasma was separated immediately by centrifugation at 4 °C and stored in aliquots at –80 °C until assayed.

Gastrin and PP were measured by radioimmunoassay using commercially available kits (Incstar Corporation, Stillwater, MN, USA, and Peninsula Laboratories, Inc., Belmont, CA, USA) as previously described (9). The upper limits of our normal ranges (mean + 3 S.D. of 100 healthy subjects aged 18–78 years) were 110 ng/l for gastrin and 57 pmol/l for PP.

Results were expressed as means ± S.E.M., with the exception of gastrin data in patients with ZES and atrophic gastritis which were given as median value and range. Statistical analysis of the data was performed by Wilcoxon and Mann-Whitney tests, using Bonferroni's correction for multiple comparisons. Pearson's test was employed to seek correlations between variables. A  $P$  value of < 0.05 was considered significant.

## Results

As shown in Table 1 there were no significant differences in mean fasting PP levels among the different groups of subjects, although the highest values (68 and 76 pmol/l) occurred in two ZES patients, one of whom had a MEN I. These values were above the upper limit of our normal range (57 pmol/l).

Secretin stimulated PP release in all the subjects (Table 1). Peak values were similar in the different groups of subjects and usually occurred 5 min after injection (range 2–10 min).

There were no significant correlations between PP response to secretin, expressed as both  $\Delta$  peaks and areas under the curve (AUC), and other variables considered, including subject age, basal PP levels, and gastrin basal levels and AUCs after secretin.

## Discussion

In agreement with previous findings (4, 6, 7), our results clearly demonstrate that in humans secretin, given at pharmacological doses as an i.v. bolus, is a powerful stimulus for PP release. This does not imply that secretin plays a role in the physiological control of PP secretion. Indeed, conflicting and even negative data have been reported when secretin was given at submaximal doses or as slow infusions (2, 5, 8).

In our ZES patients the secretin/basal PP ratio was  $4.2 \pm 0.95$ , a figure similar to that of  $2.7 \pm 0.36$  obtained by Rigaud *et al.* (2) in 26 untreated ZES patients. This response, however, cannot be regarded as a paradoxical one, since we found similar increments in patients with normo- and hypergastrinemia, and also in healthy subjects. Moreover, there was no significant difference in the PP pattern between patients with and without MEN I, the peak values being  $121 \pm 19.9$  and  $98 \pm 20.9$  pmol/l respectively.

High PP fasting levels have been reported in 10–77% of patients with gut apudomas (10–14) and it has also been suggested that the finding of elevated peptide levels could be a marker for endocrine pancreatic tumors in patients with MEN I (10, 13, 15). In our series 20% of ZES patients showed basal PP levels which were definitely supranormal, but lower than 300 pmol/l, which is the suggested cut-off value for endocrine pancreatic tumors (12). Moreover, only one out of our four MEN I patients had elevated plasma PP levels, thus confirming the suggestion that high fasting plasma PP levels are a relatively insensitive marker for endocrine pancreatic tumors (13, 14).

The secretin test does not improve the diagnostic sensitivity of PP determination but the plasma PP response to a meal can be exaggerated in MEN I patients (15). On the other hand, it is obvious that in MEN I

patients without clinical evidence of gut apudomas the finding of high fasting or postprandial plasma PP levels must direct imaging studies.

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