

# Comparison of intraduodenal and intravenous administration of amino acids on gastric secretion in healthy subjects and patients with duodenal ulcer

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**SUMMARY** The ability of an amino acid mixture given intraduodenally or intravenously to stimulate gastric secretion is compared in healthy subjects and in duodenal ulcer patients. Graded amounts of amino acids by both routes produced a similar increase in acid output in healthy subjects, reaching about 30% of the maximal response to pentagastrin. Serum gastrin concentrations remained virtually unchanged but serum alpha amino acid nitrogen levels were about twice as high with intravenous as with intraduodenal administration. Intravenously administered amino acids produced a significantly higher acid output in patients with duodenal ulcer than in healthy subjects, but did not produce a significant increase in gastric acid or pepsin secretion when combined with a pentagastrin infusion as compared with pentagastrin alone. Cimetidine (2 mg/kg/h) added to intravenous amino acid infusions caused almost complete suppression of acid secretion. This study indicates that amino acids are capable of stimulating gastric secretion after intraduodenal and after intravenous administration. The response to the latter is significantly higher in patients with duodenal ulcer than in healthy subjects, does not appear to involve gastrin release, is not affected by pentagastrin, and is strongly suppressed by histamine H<sup>2</sup>-blocker.

Previous studies have shown conclusively that the only known chemicals in food that stimulate gastric secretion are products of protein digestion, peptides and amino acids. The stimulation of gastric secretion by peptic digests has been attributed to the release of gastrin from the antral and intestinal G cells (Strunz *et al.*, 1977) and to a direct action on the oxyntic glands (Konturek *et al.*, 1976). Unexpectedly, it has been reported recently that an amino acid mixture may stimulate gastric secretion after intravenous administration, without mediation of gastrointestinal hormones (Landor *et al.*, 1977; Landor and Elpidio, 1977; Landor and Ipapo, 1977).

In this report, the effect of an amino acid mixture given intraduodenally on gastric acid secretion has been compared to that evoked by intravenous amino acids in patients with duodenal ulcer and in healthy subjects.

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Received for publication 4 May 1978

## Methods

### SUBJECTS

Studies were carried out on 18 healthy male subjects with a mean age of 20 years (range 19-22 years) and a mean weight of 67 kg (range 62-75 kg), and 18 male patients with a mean age of 21 years (range 21-23 years) and a mean weight of 66 kg (range 64-69 kg) with well-established chronic duodenal ulcer disease. All patients were in clinical remission when their study period began. Each subject gave informed consent.

Intraduodenal infusions were given *via* a double lumen gastroduodenal tube modified with two balloons. A few hours after being passed the tip was positioned at the junction of the third and fourth parts of the duodenum under fluoroscopic control and the balloons straddling the pylorus were inflated with 20 ml of air to prevent duodenogastric reflux. This caused no sensation or discomfort. The duodenal lumen was used to instill the test solution into the duodenum and the gastric lumen to aspirate gastric content (Konturek *et al.*,

1978). In tests involving intravenous infusions, gastric juice was collected in 15 minute aliquots by a standard aspiration technique previously described (Konturek *et al.*, 1975).

The volume of gastric aspirates was recorded for every 15 minute period. The acidity of the gastric juice was measured by titrating 0.2 ml samples with 0.1 N NaOH using an automatic titrator (Autoburet, Radiometer, Copenhagen) and expressed in millimoles (mmol) per 30 minute periods. The pepsin concentration in the gastric juice was determined using a modification (Northrop *et al.*, 1948) of the Anson haemoglobin method (Anson, 1938). Pepsin outputs were expressed as milligrams of pepsin per 30 minute periods.

Several series of secretory tests were performed on separate groups of subjects:

1 The amino acid mixture was infused in graded amounts either intraduodenally or intravenously in four healthy subjects, control data being obtained by the infusion of 0.15 M saline.

2 The amino acid mixture was infused intravenously in graded amounts in eight healthy subjects and eight patients with duodenal ulcer.

3 Pentagastrin was infused intravenously either alone or in combination with the amino acid mixture given in graded amounts into six healthy subjects and six patients with duodenal ulcer.

4 The amino acid mixture was infused intravenously in graded amounts either alone or in combination with cimetidine-hydrochloride in a constant dose (2 mg/kg/h) given throughout the test in four patients with duodenal ulcer.

5 Maximal acid secretory response to penta-gastrin (2 µg/kg/h) given intravenously was determined in each subject and the acid secretory response to the amino acid mixture was expressed as a percentage of this pentagastrin maximum.

In all tests, the amino acid mixture consisting of L-isomers of crystalline amino acids was made up to simulate the composition described by White *et al.* (1954) of 5% bovine serum albumin, adjusted to pH 7.0 and to an osmolality of about 300 mOsm/kg. The rate of infusion was increased twofold every 60 minutes so that amounts could be delivered that varied from 60 to 480 ml/h in a one-day test.

Blood samples for gastrin, insulin, growth hormone (HGH), alpha amino acids, nitrogen, and glucose determinations were obtained from a peripheral vein under basal conditions and at the end of each rate of amino acid infusion. Serum gastrin was measured by radioimmunoassay (Yalow and Berson, 1970). Antibodies to gastrin were obtained by immunising rabbits with synthetic human gastrin I (G-2-17) (ICI, England) covalently

coupled to bovine serum albumin according to McGuigan (1968) and used in a final dilution of 1 : 300 000. Monoiodinated synthetic human gastrin I (G-17) was used as tracer and G-17 as standard. The separation of antibody-bound from free hormone was carried out by dextran-coated charcoal and the labelled free and bound hormone was counted in an automatic gamma scintillation counter (Wallac, LKB, Sweden). The antibody used in this study was immunoreactive with all known molecular forms of gastrin. All determinations were made in duplicate. The immunoassay system was sufficiently sensitive to detect 5 pg/ml of serum gastrin. Intra-assay variation was 9% and interassay variation was 16%. Serum growth hormone (Schalch and Parker, 1964) and insulin (Herbert *et al.*, 1965) levels also were determined by radioimmunoassay, alpha amino acid nitrogen levels by ninhydrin method (White *et al.*, 1954) and blood glucose by a modified Nelson method (Reinhold, 1953).

Results are expressed as the mean  $\pm$  SEM. Student's *t* test was used to determine the significance of differences between the means, with differences giving a *P* value of less than 0.05 being considered significant (Snedecor, 1956).

## Results

### COMPARISON OF GASTRIC ACID STIMULATION BY INTRADUODENAL AND INTRAVENOUS ADMINISTRATION OF AMINO ACIDS IN HEALTHY SUBJECTS

The amino acid mixture infused intraduodenally or intravenously at stepwise increasing rates in four healthy subjects caused graded increase in gastric acid secretion (Fig. 1). The response at a given rate reached a peak within about 60 minutes. The sum of the last two 15 minute outputs at each infusion rate was used to construct the dose response curves shown. The peak acid secretion was not significantly different whether amino acid mixture was administered intravenously or intraduodenally and amounted to about 32% of the maximal response to pentagastrin ( $11.6 \pm 1.3$  mmol/30 min) in these subjects. The mean concentration of gastrin was  $64 \pm 9$  pg/ml under basal conditions and did not change significantly. The mean serum alpha amino acid nitrogen concentration was  $1.57 \pm 0.21$  mmol/l under basal conditions and showed a dose-dependent increase with the response to intravenous amino acid administration being approximately twice that observed with intraduodenal amino acid administration (Fig. 1).

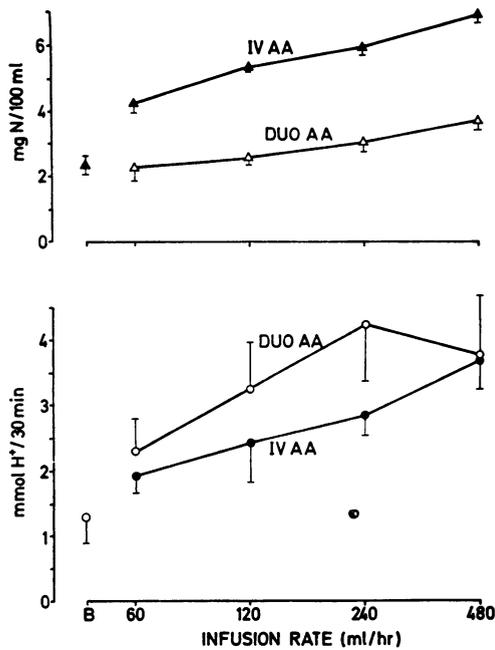


Fig. 1 The effect of intraduodenal (DUO) or intravenous (IV) amino acid infusions in graded amounts on gastric acid secretion and serum alpha amino acid nitrogen level in four healthy subjects. Means  $\pm$  SEM of four tests.

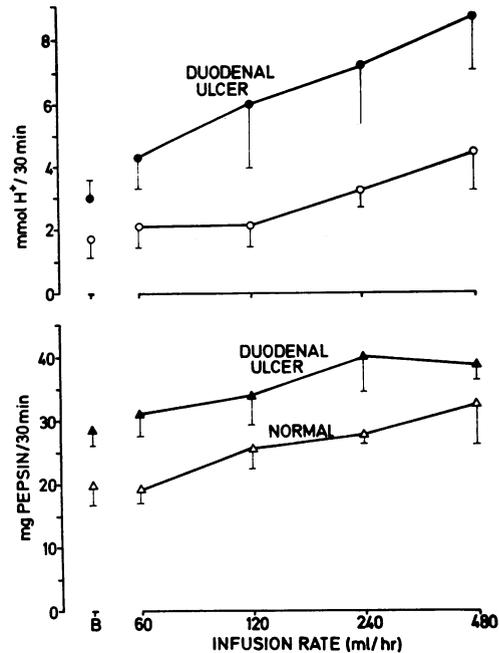


Fig. 2 Effect of intravenous amino acid infusion in graded amounts on gastric acid and pepsin secretions in eight healthy subjects and in eight patients with duodenal ulcer. Means  $\pm$  SEM of eight tests.

COMPARISON OF GASTRIC ACID STIMULATION BY INTRAVENOUS AMINO ACIDS IN HEALTHY SUBJECTS AND PATIENTS WITH DUODENAL ULCER

Intravenous infusion of the amino acid mixture in graded amounts caused a dose-dependent increase

in gastric acid output in both groups (Fig. 2). The peak acid output in healthy subjects and in patients with duodenal ulcer reached, respectively, 33% and 56% of the pentagastrin maximum. This difference was statistically significant. Intravenous amino acid infusion resulted in a marked rise in pepsin

Table Effects of intravenous infusion of graded amounts of amino acid mixture on serum concentrations of alpha amino acid nitrogen, gastrin, insulin, and HGH, and on blood glucose levels in eight normal subjects and eight patients with duodenal ulcer

|                                     | Basal           | Intravenous infusion of amino acid mixture |                  |                  |                  |
|-------------------------------------|-----------------|--|------------------|------------------|------------------|
|                                     |                 | 60 ml/h                                    | 120 ml/h         | 240 ml/h         | 480 ml/h         |
| <i>Healthy subjects</i>             |                 |  |                  |                  |                  |
| Amino acid nitrogen (mmol/l)        | 2.64 $\pm$ 0.64 | 4.21 $\pm$ 1.35                            | 7.14 $\pm$ 2.30* | 7.28 $\pm$ 2.57* | 8.42 $\pm$ 2.85* |
| Blood glucose (mmol/l)              | 4.96 $\pm$ 0.13 | 4.97 $\pm$ 0.11                            | 5.00 $\pm$ 0.16  | 5.21 $\pm$ 0.27  | 5.26 $\pm$ 0.33  |
| Gastrin (pg/ml)                     | 75 $\pm$ 9      | 80 $\pm$ 13                                | 72 $\pm$ 8       | 68 $\pm$ 10      | 67 $\pm$ 9       |
| Insulin (uU/ml)                     | 15.8 $\pm$ 3.0  | 20.4 $\pm$ 1.8                             | 21.1 $\pm$ 3.1*  | 32.0 $\pm$ 5.3*  | 40.1 $\pm$ 7.7*  |
| HGH (ng/ml)                         | 3.8 $\pm$ 1.1   | 6.7 $\pm$ 1.7                              | 5.9 $\pm$ 1.3*   | 4.4 $\pm$ 0.3    | 6.9 $\pm$ 0.5*   |
| <i>Patients with duodenal ulcer</i> |                 |  |                  |                  |                  |
| Amino acid nitrogen (mmol/l)        | 3.07 $\pm$ 1.07 | 3.78 $\pm$ 0.78                            | 7.28 $\pm$ 2.42* | 7.85 $\pm$ 1.92* | 9.71 $\pm$ 2.85* |
| Blood glucose (mmol/l)              | 5.61 $\pm$ 0.32 | 5.45 $\pm$ 0.40                            | 5.28 $\pm$ 0.27  | 5.69 $\pm$ 0.40  | 6.03 $\pm$ 0.81  |
| Gastrin (pg/ml)                     | 69 $\pm$ 6      | 72 $\pm$ 8                                 | 64 $\pm$ 11      | 70 $\pm$ 8       | 75 $\pm$ 12      |
| Insulin (uU/ml)                     | 13.7 $\pm$ 6.4  | 19.5 $\pm$ 2.2*                            | 19.2 $\pm$ 7.6*  | 2.18 $\pm$ 7.4*  | 26.3 $\pm$ 7.4*  |
| HGH (ng/ml)                         | 4.3 $\pm$ 1.5   | 5.3 $\pm$ 1.1                              | 7.8 $\pm$ 2.8*   | 7.2 $\pm$ 2.4*   | 8.6 $\pm$ 2.6*   |

\* Significant increase above basal.

secretion both in healthy subjects and in patients with duodenal ulcer and the difference between the two groups was not statistically significant (Fig. 2). Serum gastrin, insulin, HGH, and alpha amino acid nitrogen concentrations are shown in the Table. Serum gastrin levels did not change significantly in either group of subjects. Both insulin and HGH rose in a dose-dependent manner in both groups of subjects and alpha amino acid nitrogen levels also showed a tendency to increase with increasing rates of infusion. Blood glucose levels remained unchanged.

The gastric acid and pepsin response to intravenous amino acids combined with pentagastrin was not significantly different from that obtained with pentagastrin alone in either group (Fig. 3).

Cimetidine, a histamine H<sub>2</sub>-blocker, added to intravenous infusions of graded amounts of amino acid mixture in four patients with duodenal ulcer resulted in almost complete suppression of gastric acid secretion (Fig. 4).

## Discussion

This study shows that the amino acid mixture given intravenously stimulated gastric acid and pepsin secretion and that the response was significantly higher in patients with duodenal ulcer than in healthy subjects.

Originally, the stimulatory effect of intravenous amino acids on gastric secretion was observed in dogs (Okada *et al.*, 1930; Landor *et al.*, 1977; Landor and Elpidio, 1977; Landor and Ipapo, 1977) in which the response was of similar magnitude to

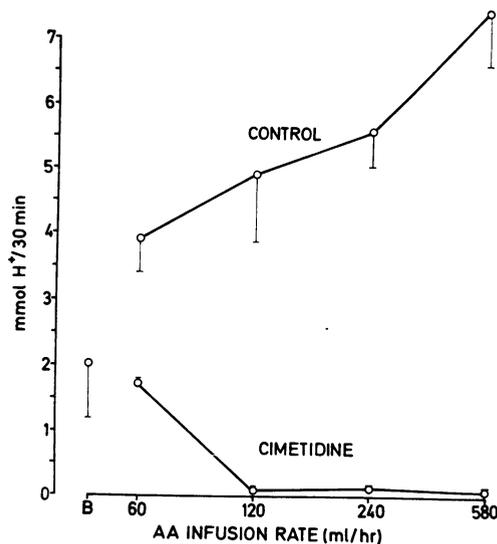


Fig. 4 Effect of cimetidine (2 mg/kg/h) given intravenously on the gastric acid response to intravenous infusion of graded amounts of amino acid mixture. In control tests amino acid mixture was given alone.

that caused by intrajejunal administration of the same amino acid solution. This suggested that it was amino acid mixture absorbed from the gut into the circulation which might account for a major portion of the intestinal phase of gastric secretion. In addition, it was found that the stimulation by intravenous amino acids persisted after removal of the antrum, duodenum, jejunum, ileum, and

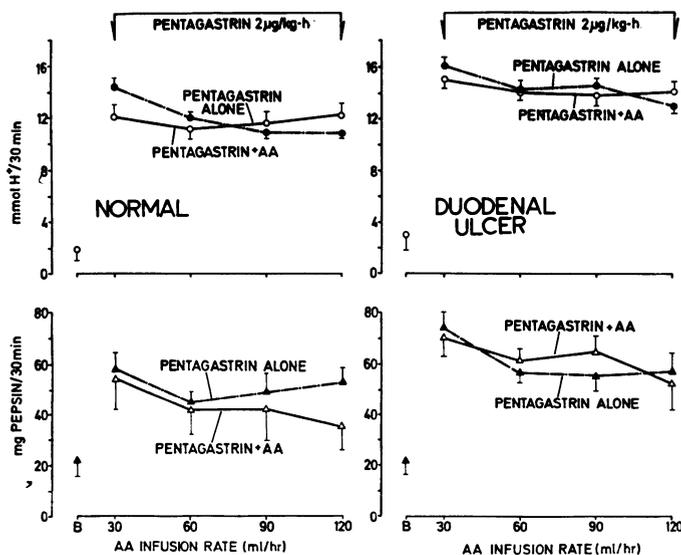


Fig. 3 Gastric acid and pepsin secretions in response to intravenous infusion of pentagastrin alone and in combination with increasing amounts of amino acid mixture in eight healthy subjects and eight patients with duodenal ulcer. Means  $\pm$  SEM of eight tests.

pancreas (all known sources of gastrointestinal hormones), indicating that amino acids act directly on the oxyntic cells to stimulate acid production.

In man, the stimulation of gastric secretion by intravenous amino acids was first reported in 1930 by Okada *et al.* and then by Demling and Classen (1971) and Isenberg and Maxwell (1978) who found a result equal to about 30% of the peak response induced by pentagastrin. This was not accompanied by any change in serum gastrin and was attributed to a direct action of amino acids on the oxyntic glands.

Our present report confirms previous observations that intravenous amino acids are capable of stimulating the gastric secretion of acid and pepsin without affecting serum gastrin level. Indeed, the gastric acid response to intravenous amino acids was not significantly different from that obtained by intraduodenal administration of the same amino acid mixture in normal subjects. However, this does not mean that amino acids stimulate gastric secretion solely after being absorbed from the gut, because most are probably taken up during passage through the liver. This is supported by a previous finding in animals that amino acids given intraperitoneally were less potent than amino acids given systemically (Landor *et al.*, 1977) and by the finding of this study that the increase of serum amino acid concentrations after intraduodenal administration was only about half that during systemic intravenous amino acid infusion.

The mechanism of gastric acid stimulation by intravenous amino acids has not been elucidated. Gastrin does not appear to be involved, as the serum gastrin concentration remained unchanged. We also failed to observe any significant increase in serum gastrin during duodenal perfusion of amino acid mixture, although human duodenum was found previously to contain small amounts of gastrin (Malmström *et al.*, 1976). However, in dogs, liver extract meal instilled into the duodenum was reported (Konturek *et al.*, 1976) to release significant amounts of gastrin, which could contribute to the marked stimulation of gastric secretion by intestinal meal in this species. These observations suggest that there are species differences in gastrin release in response to duodenal meal between man and dog and that in dog, but not in man, duodenal meal releases gastrin.

The increase in serum HGH and insulin level during intravenous amino acid infusion might suggest that these hormones could contribute to gastric stimulation, as recent studies in rats have shown a close relationship between growth hormone and gastrin, indicating that gastrin production and synthesis could be regulated by growth hormone

(Enochs and Johnson, 1975; Johnson, 1976). However, there is no evidence that growth hormone can stimulate gastric acid secretion in man. Furthermore, while insulin stimulates both gastric secretion and gastrin release, these effects occur only when the blood glucose is reduced and this did not occur in the present study.

The suppression of amino acid-induced gastric acid secretion by cimetidine, an H<sub>2</sub>-blocker, suggests that the stimulation of gastric secretion by amino acids could be, at least in part, mediated by histamine and H<sub>2</sub>-receptors on the oxyntic cells. Histidine in the amino acid mixture can be transformed to histamine and was found, in animal experiments, to be the most potent gastric stimulant among amino acids (Konturek *et al.*, 1976). The almost complete inhibition of acid secretion in response to amino acids indicates that cimetidine is an effective inhibitor of stimulation induced by other amino acids. Furthermore, it is difficult to be confident about the specificity of its action because this drug is known to block acid secretion regardless of whether the secretion is induced by histamine, gastrin, cholinergic agents, or a meal (Konturek *et al.*, 1974).

Our study demonstrates that patients with duodenal ulcer showed a significantly higher gastric acid response than did healthy subjects. This suggests that, during intravenous amino acid stimulation, as during cephalic, gastric, and intestinal stimulation (Konturek, 1976), the oxyntic cells react more vigorously in patients with duodenal ulcer. Because of the small number involved it is not known whether this represents a general feature of duodenal ulcer disease or an entity occurring only in some patients with duodenal ulcer.

It is of interest that intestinal phase stimulation of gastric secretion by liver extract meal instilled into the duodenum in animals (Konturek, 1977) and by amino acid mixture in man (Konturek *et al.*, 1978) caused a marked augmentation of the maximal response to pentagastrin or histamine—probably due to interaction of specific intestinal phase hormone, entero-oxyntin, with these exogenous stimulants. Again patients with duodenal ulcer exhibited more marked and prolonged augmentation to the combination than healthy subjects. The present study shows that intravenous amino acid infusion does not augment the gastric acid or pepsin responses to pentagastrin either in healthy subjects or in patients with duodenal ulcer. This again indicates that the intravenous infusion of amino acids excites the oxyntic cells *via* different mechanisms from that during the intestinal phase stimulation of gastric secretion.

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