

ENHANCEMENT OF PENTAGASTRIN-INDUCED GASTRIC ACID SECRETION BY CLONIDINE IN THE CONSCIOUS DOG

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The effect of intravenous clonidine on pentagastrin-induced gastric acid secretion has been studied in conscious dogs with Heidenhain pouches. Dose-dependent enhancement of secretion was found in response to clonidine (5-20 $\mu\text{g/kg}$). Clonidine (20 $\mu\text{g/kg}$) increased the maximal secretory rate to pentagastrin to a value not significantly different from the maximal response to histamine.

Introduction

In conscious pylorus-ligated rats the anti-hypertensive agent clonidine has been reported to decrease the volume and acidity of the gastric contents and to reduce reserpine-induced gastric ulceration (Hoefke & Kobinger, 1966; Walz & van Zwieten, 1970; Brodie, Lotti & Bauer, 1970). Brodie *et al.* (1970) however found that secretion-inhibiting doses of clonidine did not reduce gastric haemorrhage caused by cold plus restraint. In contrast, large intravenous doses of clonidine have been shown to cause increases in acid secretion in the perfused stomachs of anaesthetized rats and guinea-pigs (Walz & van Zwieten, 1970). Clonidine was found to decrease basal and pentagastrin-induced gastric secretion in normal (Ottenjann, 1968; Kaess & von Mickulicz-Radecki, 1971) and hypersecretory (Neuhaus & Humpert, 1968) human subjects.

Clonidine has been shown to decrease central sympathetic efferent discharge and to exert a peripheral adrenergic-neurone blocking action (Schmitt, 1970; Briant & Reid, 1972; Werner, Starke & Schümann, 1972; Armstrong & Boura, 1973). Curwain & Holton (1972) reported that both α - and β -adrenoceptor agonists inhibit gastric acid secretion in response to pentagastrin in conscious dogs. We have studied the effects of intravenous clonidine on pentagastrin-induced gastric acid secretion in conscious dogs with Heidenhain pouches since it might reasonably be expected that clonidine, by reducing the adrenergic influences on the gastric mucosa would cause an enhancement of the secretory response.

Methods

Five healthy bitches (14-23 kg) with well-established Heidenhain gastric pouches were used. Food was withheld but water allowed for 18 h before each experiment. Acid secretion from the pouch was measured as previously described (Curwain & Holton, 1972). In some experiments gastric mucosal blood flow was estimated by ^3H -aniline clearance (Curwain & Holton, 1973).

In the first series of 11 experiments in three dogs pentagastrin was infused to give a secretory rate of approximately 40% of the maximal response to histamine. Clonidine (5, 10 or 20 $\mu\text{g/kg}$) was administered over 15-30 min with the pentagastrin infusion during the secretory plateau. Gastric juice collection was continued throughout the clonidine infusion and afterwards until the rate of secretion had returned towards control levels.

In the second series of six experiments in five dogs increasing doses of pentagastrin were infused until the maximal secretory rate was achieved. The effect of clonidine (20 $\mu\text{g/kg}$) given over 30 min was then observed.

Results were expressed as follows. For each dog the maximal acid secretory response of the pouch to histamine had been previously determined. During these determinations mepyramine (12.5-25 mg at 30 min intervals) was used to minimize the side effects of histamine. Acid secretion during the clonidine experiments was calculated in $\mu\text{mol H}^+/\text{min}$ and subsequently expressed as a percentage of the maximal response to histamine. The control rate of secretion was defined as the mean of the rates during the three 15 min periods immediately preceding the administration of clonidine. The first sample collected after starting the clonidine infusion was discarded and the response calculated from the next four collections.

Results

First series of experiments. Administration of clonidine (5, 10 or 20 $\mu\text{g/kg}$) caused a dose-related

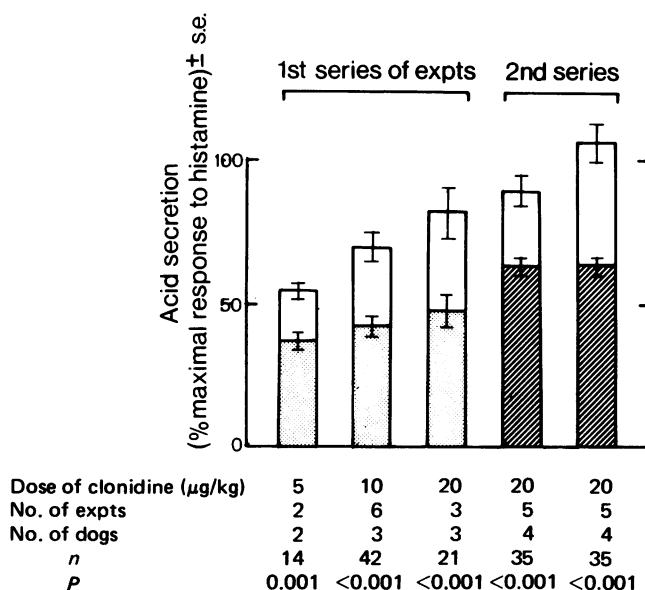


Fig. 1 The effect of intravenous clonidine on pentagastrin-induced gastric acid secretion in conscious dogs with Heidenhain pouches. The shaded areas denote control secretory rate, the unshaded areas denote secretory rate after clonidine administration calculated as described in methods section. *P* is the probability that the secretory rate after clonidine is not significantly different from the control value. *n* is the total number of observations from which *P* has been calculated. The results from the second series of experiments were processed in two ways. The left hand column shows the results calculated as described in the methods section. The right hand column shows the results using the same control values but taking into account only the peak secretory rate, from a single collection in each experiment, after clonidine administration. This was done since the peak response to clonidine in these experiments was short-lived and the normal way of expressing the results reduced the apparent size of the response. In the second series of experiments secretion after clonidine was not significantly different from the maximal response to histamine (*P* > 0.05 for both methods of calculation).

increase in acid secretion lasting up to 2.5 hours. The effects on secretion are illustrated in Figure 1. In eight of these experiments a concomitant increase in mucosal blood flow was observed, and the ratio of blood flow to secretion showed no consistent change. In two further experiments in two of the dogs, clonidine (20 µg/kg over 30 min) given in the absence of secretagogue, did not itself stimulate acid secretion.

Second series of experiments. In four of the dogs the maximal secretion in response to pentagastrin was $63\% \pm 3\%$ (s.e.) of the maximal response to histamine. When clonidine (20 µg/kg) was given during the maximal pentagastrin-induced secretion, the mean secretory rate increased to a value not significantly different from the maximal response to histamine (Figure 1).

In a fifth dog the maximal secretory response to pentagastrin was the same as that for histamine: clonidine (20 µg/kg) increased the secretory rate to 147% of the previous maximal response. In this

animal large doses of histamine caused considerable distress which was not abolished by mepyramine and would have reflexly decreased the secretory response.

Discussion

The results show that intravenous clonidine produces a dose-related increase in the rate of pentagastrin-induced acid secretion. The increase in secretion was accompanied by a concomitant increase in mucosal blood flow. The ratio of blood flow to secretion showed no consistent change and it is unlikely that the observed increase in secretion was the direct result of a change in mucosal blood flow.

Catecholamines inhibit canine gastric acid secretion in response to pentagastrin (see Holton, 1973, for references). This inhibition may be secondary to vasoconstriction of the gastric mucosal vascula-

ture, an α -adrenoceptor effect, or be a direct action on the secretory apparatus, a β -adrenoceptor effect (Curwain & Holton, 1972). The increases in secretion observed following administration of clonidine may be due to a reduction in sympathetic influence on the gastric mucosa. Werner *et al.* (1972) have reported a peripheral adrenergic-neurone blocking action of clonidine. It has also been shown that clonidine has a central action, reducing the rate of bulbar sympathetic efferent discharge. Schmitt (1970) has described the stimulation of central post-synaptic α -adrenoceptors by clonidine, and a pre-synaptic noradrenergic-neurone blocking action has also been reported (Briant & Reid, 1972). Any, or all, of these mechanisms may account for a reduction in sympathetic influence on the gastric mucosa. This effect may be mediated directly through the sympathetic nerves to the stomach or indirectly via the adrenal medulla. It is relevant that Hökfelt, Hedeland & Dymling (1970) have reported a fall in plasma and urinary catecholamines in a young human male evident within 2 h of the intravenous administration of clonidine (150 μ g/kg).

It has been suggested that pentagastrin-induced acid secretion is mediated by endogenous histamine (Code, 1956; Kahlson, Rosengren & Svensson, 1973). The difference between the maximal rates of secretion in response to pentagastrin and histamine that we obtained is in agreement with that found by Konturek & Grossman (1966). β -Adrenoceptor stimulants inhibit histamine-forming capacity in human leucocytes (Assem & Feigenbaum, 1972) and in rat gastric mucosa (Svensson, personal communication) and gastric mucosal histamine-forming capacity may normally be limited by sympathetic tone. The secretory response to exogenous histamine would not be subject to this restraint. It is therefore likely that enhancement by clonidine of the secretory response to pentagastrin is mediated by reduction in sympathetic tone which in turn may inhibit secretion by vasoconstriction or by reduction of mucosal histamine-forming capacity. A further possibility is that clonidine may directly facilitate the stimulation of the mucosal histamine-forming apparatus.

The results described agree with those observed in anaesthetized rats and guinea-pigs by Walz & van Zwieten (1970). However, they differ from the decreases in gastric acid secretion reported in conscious pylorus-ligated rats and in the conscious and unconscious human. Pyloric ligation involves induction of and recovery from anaesthesia and some intra-abdominal manipulations. The differences in circulating hormones likely to be associated with such procedures and also with the unconscious state of the patients described by

Neuhaus & Humpert (1968) may account for the difference in effect seen. In human subjects diminished sympathetic influence increases gastric emptying and may produce an artefactual decrease in the volume of gastric juice collected with a naso-gastric cannula. This may contribute to the results obtained with clonidine.

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