

## *Effect of nicardipine on gastric acid secretion in man*

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### SUMMARY

The effect of nicardipine on basal and pentagastrin-stimulated gastric acid secretion in normal volunteers was investigated. When compared with saline, an intravenous infusion of nicardipine caused a significant decrease in peak acid output (from 37.8 mmol hour<sup>-1</sup> to 28.8 mmol hour<sup>-1</sup>;  $P = 0.04$ ) and a small reduction in aspirate volume. Nicardipine had no significant action on basal acid output or volume of aspirate. Proteolytic activity in both the basal and stimulated periods was unaffected by nicardipine as were serum gastrin concentrations. Although calcium channel blocking agents are theoretically antisecretory the present study suggests they are unlikely to have clinically useful therapeutic actions.

### INTRODUCTION

In recent years the cellular mechanisms underlying the secretion of gastric acid have become more clearly understood. It is now recognized that the parietal cell possesses separate receptors for histamine, acetylcholine and gastrin and that the intracellular mediators of receptor activation differ for these secretagogues.<sup>1</sup> The stimulation of the parietal cell by both acetylcholine and gastrin is dependent upon an increase in cytosolic calcium.<sup>2</sup> After cholinergic stimulation this increase is

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thought to occur because of an influx of calcium ions across the cell membrane, whereas the mechanism by which gastrin acts to increase intracellular calcium remains unclear.<sup>3,4</sup> Calcium channel blocking agents might theoretically therefore possess antisecretory actions. The purpose of the present study was to investigate the effect of nicardipine, a dihydropyridine calcium antagonist, on basal and pentagastrin stimulated acid production in man.

## SUBJECTS AND METHODS

Six healthy male volunteers (age range 19–23 years) were studied. All were non-smokers. Each subject attended on two occasions separated by at least 7 days and received in random order an intravenous infusion of either 0.9% saline or nicardipine (5 mg hour<sup>-1</sup>), both administered at a rate of 20 ml hour<sup>-1</sup>. Following an overnight fast, a nasogastric tube was positioned in the stomach and the infusion of nicardipine or saline commenced. The gastric aspirate for the first 30 min was discarded and then four 15 min basal aliquots were collected. Subcutaneous pentagastrin (6 µg kg<sup>-1</sup>) was then given and 15 min aliquots measured for a further 60 min. Blood was taken for serum gastrin estimation at 15 min intervals up to the time of pentagastrin administration and the subjects pulse and blood pressure monitored throughout the study. The volume of each sample of gastric aspirate was recorded together with the titratable acid (against 0.1 M NaOH) and proteolytic activity, and the basal and peak acid output calculated. Statistical analysis was performed using an analysis of variance appropriate to the two-period cross-over design.<sup>5</sup> All tests were two sided and at the 5% level of significance. Each subject gave written consent before entering the study, which was approved by the hospital's ethical committee.

## RESULTS

In the basal phase of the study no significant difference between nicardipine and saline occurred in terms of volume of aspirate. Nicardipine caused a 32% decrease in basal acid output (from 5.3 mmol hour<sup>-1</sup> to 3.6 mmol hour<sup>-1</sup>) but this failed to reach statistical significance. However, following pentagastrin stimulation, treatment with nicardipine caused a significant decrease in peak acid output (from 37.8 mmol hour<sup>-1</sup> to 28.8 mmol hour<sup>-1</sup>;  $P = 0.04$ ) (Figure 1). This was accompanied by a non-significant decrease in the volume of aspirate (Figure 2).

A decrease in proteolytic activity following pentagastrin administration occurred with both saline and nicardipine, but no significant difference between the two treatments was observed. Nicardipine caused no significant change in the basal serum gastrin concentration.

Infusion of nicardipine was associated with an increase in heart rate (73 compared with 84 beats min<sup>-1</sup>) but no change in blood pressure. It was well tolerated by all subjects.

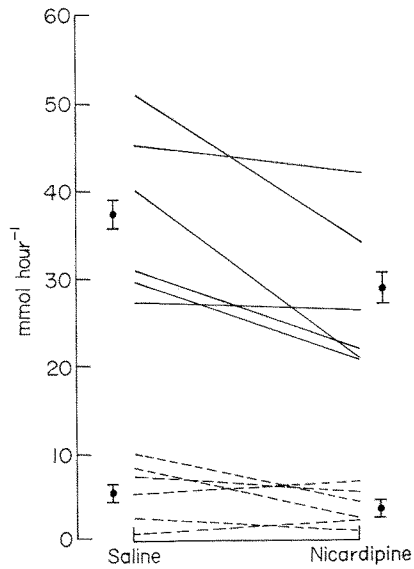


Figure 1. Effect of nicardipine on basal and peak acid output in six healthy volunteers. —, peak acid output; ---, basal acid output. Bars indicate mean  $\pm$  S.E.M.

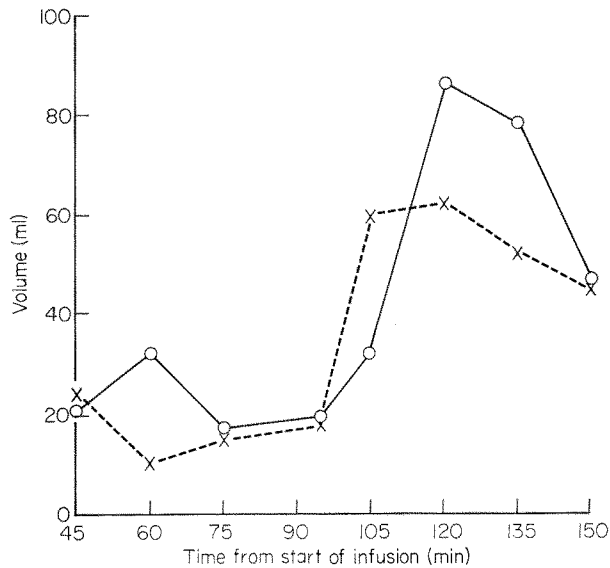


Figure 2. Effect of nicardipine on the mean volume of gastric aspirate in six healthy volunteers. —○—, 0.9% saline; —x—, nicardipine.

## DISCUSSION

The present study demonstrates that treatment with i.v. nicardipine causes a significant decrease ( $P = 0.04$ ) in peak acid output following maximal pentagastrin stimulation, but it has no significant effect on basal acid output, proteolytic activity of gastric juice or basal serum gastrin concentration.

Although there have been no previous reports on the effect of nicardipine on gastric acid secretion in man, studies concerning the actions of both verapamil<sup>6-9</sup>

and nifedipine<sup>10,11</sup> have been reported recently. These studies are difficult to compare, as varying doses of pentagastrin or gastrin have been used and the drugs have been administered at different doses and by a variety of routes. It is impossible to assess whether the different agents have attained similar degrees of calcium channel blockade.

Verapamil appears to have little effect on basal acid output, but studies have produced variable results when stimulated output is considered. To some extent this may reflect the dose of stimulatory agent and verapamil which was administered. Levine *et al.*<sup>6</sup> showed no effect of low-dose verapamil infusion on high-dose pentagastrin stimulation, whereas using a higher dose of verapamil and lower doses of pentagastrin, Sonnenberg *et al.*<sup>7</sup> found a significant decrease in acid output. Kirkegaard *et al.*<sup>8</sup> noted that a low-dose verapamil infusion inhibited acid secretion stimulated by low-dose, but not high-dose, leucine synthetic human gastrin. However, Aadland *et al.*<sup>9</sup> found no significant change in stimulated acid output despite using high-dose verapamil and low-dose pentagastrin.

Nifedipine is, like nifedipine, a dihydropyridine calcium antagonist, and has been found to decrease basal acid output and that stimulated by low-dose, but not high-dose, pentagastrin.<sup>10,11</sup> This is therefore at variance with the results of the present study in that we noted a significant decrease in acid output following maximal pentagastrin stimulation. This may result from the different route used to administer the two drugs. The decrease in basal acid output seen in the present study was not statistically significant, although it was of similar magnitude to that noted with nifedipine<sup>11</sup> (nifedipine 32%, nifedipine 37%).

Calcium channel blocking agents do therefore appear to cause some decrease in acid output following pentagastrin stimulation, supporting the model of a calcium mediated gastrinergic receptor. The effect of calcium channel blocking agents on acid output following cholinergic stimulation would also be of interest, as the influx of calcium ions across the cell membrane is known to be of importance in isolated parietal cell preparations.<sup>3,4</sup> Initial studies have revealed that verapamil produces little inhibition of acid output following sham feeding,<sup>7</sup> but this deserves further evaluation.

Thus the present study provides support that calcium antagonists do cause a modest decrease of gastric acid output. However, this does not approach the magnitude of that achieved by the H<sub>2</sub>-receptor antagonists. Therefore, calcium channel blocking agents are unlikely to be of clinical use unless they exert a potentiating effect with other ulcer-healing agents.

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