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THE EFFECT OF β-ADRENOCEPTOR AGONISTS AND ANTAGONISTS ON GASTRIC EMPTYING IN MAN

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1 The effect of β-adrenoceptor agonists and antagonists on gastric emptying of a solid meal labelled wth Indium^{113m} was measured by a gamma camera in healthy volunteers or patients with hypertension. Each subject acted as his own control.

2 In ten subjects given isoprenaline (10 or 20 mg) sublingually 30 min before the meal, gastric emptying half-times were significantly prolonged ($P < 0.05$). No effect was observed when isoprenaline was given immediately before the meal.

3 Salbutamol, 4 mg four times daily for 1 week also significantly prolonged gastric emptying in four subjects ($P < 0.05$).

4 The effect of isoprenaline on gastric emptying was blocked by propranolol 40 mg four times daily for 1 week.

5 In ten subjects propranolol 40 mg four times daily alone for 1 week was found to significantly speed up gastric emptying ($P < 0.005$), suggesting that emptying of the normal stomach is subject to some degree of adrenergic inhibition.

Introduction

Vagal control of gastric emptying in man has been extensively studied in recent years, but the *in vivo* role of the sympathetic innervation of gastric muscle remains largely unexplored. Similarly, the effect of cholinergic and anticholinergic drugs on gastric emptying has been studied, but not that of adrenergic drugs.

Anticholinergic drugs such as propantheline (Nimmo, Heading, Tothill & Prescott, 1973) have been shown to delay, but cholinergic drugs such as bethanechol (Hamilton, Sheiner & Quinlan, 1976) and carbachol (Tinker, Kocak & Jones, 1970) to increase the rate of gastric emptying. Drug induced alterations of gastrointestinal motility can also change drug absorption in man; e.g. metoclopramide increases the rate of gastric emptying and produces more rapid absorption of tetracycline and paracetamol (Gothoni, Pentikainen & Vapaatalo, 1972).

Studies on human isolated gastric muscle have shown that β-adrenergic receptor stimulating drugs such as isoprenaline and salbutamol inhibit gastric muscle activity (Bennett & Whitney, 1966; Hedges & Turner, 1969). It has been shown that the effect of isoprenaline on gastric muscle can be abolished by the β-adrenoceptor blocker propranolol (Hedges & Turner, 1971). The effect of these drugs on gastric emptying in man has not been studied and it is this aspect of gastrointestinal pharmacology that we set out to investigate.

Method

Twenty-six healthy volunteers and nine patients with mild hypertension about to be started on β-adrenoceptor blocking drugs were studied.

Gastric emptying was measured by monitoring the passage through the stomach of a solid test meal labelled with 1 mCi of Indium^{113m} DTPA (diethylenetriaminepentaacetic acid). This method has been described in detail previously (Howlett, Ward & Duthie, 1974). The meal consisted of meat, peas and instant mashed potato, the total weight being 250 g. The Indium was incorporated into the mashed potato. Three tablets (1.5 g) of paracetamol were crushed and taken immediately after the test meal with 10 ml of water. The subjects were rested in a semi-erect position in a dental chair and took a mean

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time of 7.5 min to eat the meal. There was a further delay of 5 min required to define the gastric area before recording commenced. Half emptying time of the meal ($T_{½}$) was computed from the best fit of a semi-logarithmic plot of the data for the common time interval of 25–60 min. Serial blood samples to estimate serum paracetamol levels were taken via an indwelling catheter.

A total of 78 studies was carried out; the order of the control meals (on no drug therapy) and meals after a drug was randomised. The reproducibility of gastric emptying times in any one individual is satisfactory, being within 15% (Howlett, 1976), but because of the large variation between individuals each subject acted as his own control. Results are shown a mean ± 1 s.e. mean and were analysed using a paired *t*-test.

Drugs studied

Isoprenaline (10 or 20 mg tablets sublingually). Five subjects received 10 mg and five subjects 20 mg isoprenaline 30 min before the meal. Three subjects received 20 mg isoprenaline immediately before the meal. Three subjects received three 20 mg doses of isoprenaline at 30, 15 and 0 min before the meal. Five subjects received 20 mg of isoprenaline 30 min before the meal and the same procedure was repeated after having been given propranolol, 40 mg four times per day, for 1 week.

Following administration of isoprenaline the pulse rate was measured for up to 40 min.

Salbutamol (4 mg tablets) Four subjects were given salbutamol 4 mg four times per day for 1 week, the last dose being given 2 h before the test meal.

Propranolol (20 or 40 mg tablets) Ten subjects were given propranolol 20 mg four times daily for 1 day, followed by 40 mg four times per day for 1 week, the last dose being taken 2 h prior to the meal.

Results

Figure 1 shows the effect of isoprenaline given 30 min before the meal. As there was no significant difference between the effect of 10 or 20 mg of isoprenaline on gastric emptying these results have been presented together. There was a significant prolongation of gastric emptying following isoprenaline. However, following the triple dose of isoprenaline there was a significantly greater prolongation of gastric emptying than following a single dose ($P < 0.02$). There was no significant effect on gastric emptying in the group given isoprenaline immediately before the meal (Control = 36.5 ± 2.5 min, isoprenaline = 35.7 ± 2.2 min, $P > 0.1$). Salbutamol also delayed gastric emptying (Figure 2).

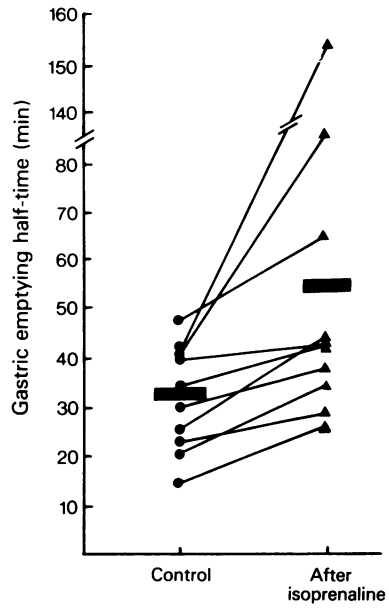

Figure 1 The effect of gastrin emptying of isoprenaline (10 or 20 mg) given sublingually 30 min before the meal. (Control, 32.2 ± 2.2 min; isoprenaline, 55.6 ± 12.8 min, $P < 0.05$).

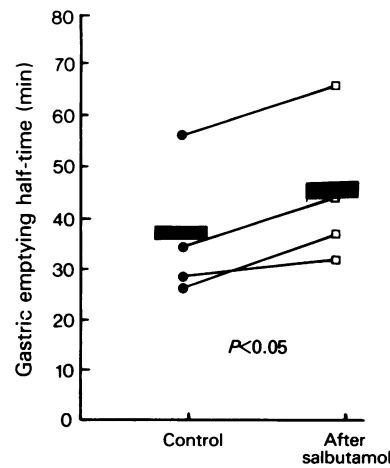

Figure 2 The effect on gastric emptying of salbutamol given 4 mg four times daily for 1 week (Control, 37.2 ± 6.5 min; salbutamol, 44.3 ± 7.8 min; $P < 0.05$).

The effect of propranolol on the action of isoprenaline is shown in Figure 3. Isoprenaline alone delayed gastric emptying in the manner previously noted, but pre-treatment with propranolol blocked this effect, there being no significant difference from control values.

In every subject propranolol alone given for 1 week

significantly speeded up gastric emptying when compared to control values (Figure 4).

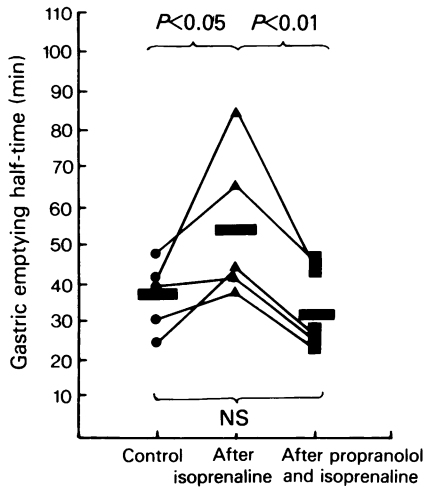

Figure 3 The effect of isoprenaline on gastric emptying before and after 7 days treatment with propranolol, 40 mg four times daily (Control, 37.2 ± 4.1 min; isoprenaline, 54.3 ± 8.1 min; isoprenaline and propranolol = 33.7 ± 4.7 min).

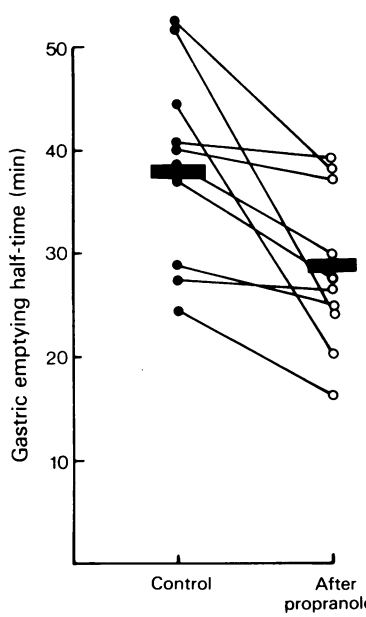

Figure 4 The effect on gastric emptying of a 1 week course of propranolol 40 mg four times daily (Control, 38.8 ± 3.0 min; propranolol, 28.6 ± 2.5 min; $P < 0.005$).

Discussion

Using our technique it was not possible to measure emptying during the first few minutes of ingestion, to differentiate between emptying of the liquid and solid components of the meal, or to study separately emptying of antrum and body of the stomach. It is, however, quite clear that both isoprenaline and salbutamol are inhibitors of gastric emptying in man. To be effective isoprenaline has to be given 30 min before the meal, as when taken immediately before eating there was no observable change in gastric emptying. In contrast the pulse rate rose significantly in every case within minutes of the administration of isoprenaline. This suggests that the inhibition of gastric emptying by sympathomimetic drugs may not be due to their direct action on smooth muscle, but through an intermediate mechanism.

Pentagastrin-induced acid secretion in dogs is decreased after administration of isoprenaline and salbutamol (Curwain, Holton & Spencer, 1972), while the same drugs reduce acid secretion and increase serum gastrin levels in rats (Lundell, Svensson & Nilsson, 1976). Similarly, adrenergic agents increase serum gastrin levels in man (Hayes, Ardill, Kennedy, Shanks & Buchanan, 1972; Stadil & Rehfeld, 1973), and as pentagastrin is a potent inhibitor of gastric emptying in man (Hamilton *et al.*, 1976) it is possible that β-adrenergic receptor drugs affect gastric emptying partly by alterations in the level of gastrin. However, there is considerable debate at present as to whether gastrin plays a role in the regulation of gastric emptying under physiological conditions (Cooke, 1975).

Our observation that the action of isoprenaline on gastric emptying can be blocked by propranolol shows that whatever the mechanism for inhibition of gastric emptying by the β-adrenoceptor agonists, this action is via β-adrenoceptors. The action of propranolol alone in speeding up gastric emptying is of considerable interest, suggesting that under physiological conditions there may be adrenergic inhibition of gastric muscle activity which may be abolished by the use of β-adrenoceptor blockers.

Adrenergic drugs are widely used in the management of bronchial asthma and β-adrenoceptor blockers such as propranolol in the treatment of angina and hypertension. The action of these drugs on gastric emptying may influence the rate of absorption of other drugs given with them (Nimmo, 1976). This aspect has been studied separately using paracetamol as the test drug and the results are being reported in the accompanying paper (Clark, Holdsworth, Howlett & Rees, 1980).

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