Short communications

The effect of betahistine on gastric acid secretion and mucosal blood flow in conscious dogs

B. P. CURWAIN, PAMELA HOLTON AND JAN SPENCER

Department of Physiology, St. Mary's Hospital Medical School (University of London), London W21 1PG

In 3 conscious dogs, betahistine (2-(2'-methyl aminoethyl pyridine)) (80 or 160 μg kg^{-1} min^{-1}) increased acid secretion from Heidenhain pouches to 8·8% and 17·6% respectively of the maximal response to histamine. Betahistine also increased mucosal blood flow (radioactive aniline clearance). The ratio of mucosal blood flow to secretion was greater for betahistine than for histamine but the difference between betahistine and histamine was significant in only one of the dogs.

Betahistine (2-(2'-methyl aminoethyl pyridine)) is chemically related to histamine and like histamine has vasodilator properties (Hunt & Fosbinder, 1942; Konzett, Bost, Bowman, Bowman & McKennis, 1971). It has been used clinically as a vasodilator for the treatment of vascular disorders (Horton, 1962; Horton & von Leden, 1962; Elia, 1966; Esser & Reis, 1968).

Patients receiving betahistine occasionally report dyspepsia as a side effect (Le Pere, 1967). Such an effect could be caused by changes in gastric secretion or motility or possibly by changes in gastric mucosal blood flow since drugs which decrease the ratio of mucosal blood flow to acid secretion are potentially ulcerogenic (Jacobson, 1965). The effect of betahistine (1 mg min^{-1}) on gastric secretion was studied by Allen, Connell, Harries & Roddie (1971) who found that it did not stimulate acid secretion in man. Haigh (personal communication) studied the effects of larger doses (70–150 μg kg^{-1} min^{-1} i.v.) of betahistine in anaesthetized dogs and found no change in total gastric blood flow, mucosal blood flow (amidopyrine clearance) or blood pressure. With one exception betahistine did not cause acid secretion. In the exceptional experiment a very small secretion was obtained in response to 150 μg kg^{-1} min^{-1}. We have extended these observations on secretion using a wide dose range of betahistine (5–160 μg kg^{-1} min^{-1} i.v.) in dogs with Heidenhain pouches. We have also studied the effect of betahistine (40–160 μg kg^{-1} min^{-1} i.v.) on gastric mucosal blood flow as measured by radioactive aniline clearance (Curwain & Holton, 1971; Curwain, 1972a).

Methods.—Three female dogs (10–14 kg) with long-established Heidenhain pouches were used in 13 experiments. Food was removed 18 h before each experiment but water was available. At the beginning of each experiment an intravenous catheter was introduced and saline (1 ml min^{-1}) was infused throughout the experiment. Drugs were added to the intravenous infusion. After a suitable control period a dose of betahistine was given for one hour after which the dose was doubled. Usually three doses of betahistine were studied in each experiment. In some experiments a small dose of histamine (0·25 μg histamine diphosphate kg^{-1} min^{-1}) or pentagastrin (0·5 μg kg^{-1} h^{-1}) was infused throughout. Gastric juice was collected at 15 min intervals and total acid was determined by titration against 0·1 N NaOH using phenolphthalein. In separate experiments, the maximal secretory response of each dog to histamine was determined.

Changes in gastric mucosal blood flow were measured in four experiments in the three dogs using the plasma clearance of radioactive aniline (Curwain & Holton, 1971; Curwain, 1972a). For this measurement, blood samples were taken at 30 min intervals via a second vein catheter and the radioactivity in 1 ml samples of plasma and gastric juice was determined. In these experiments it was necessary to ensure an acid environment at the gastric glands and so pentagastrin was infused throughout in a dose sufficient to cause acid secretion at about 10% of the maximum histamine response. In expressing the results the responses of both secretion and mucosal blood flow to pentagastrin have been taken into account.

Results.—*Acid secretion* In a total of 18 observations betahistine (5–40 μg kg^{-1} min^{-1} i.v.) did not significantly increase

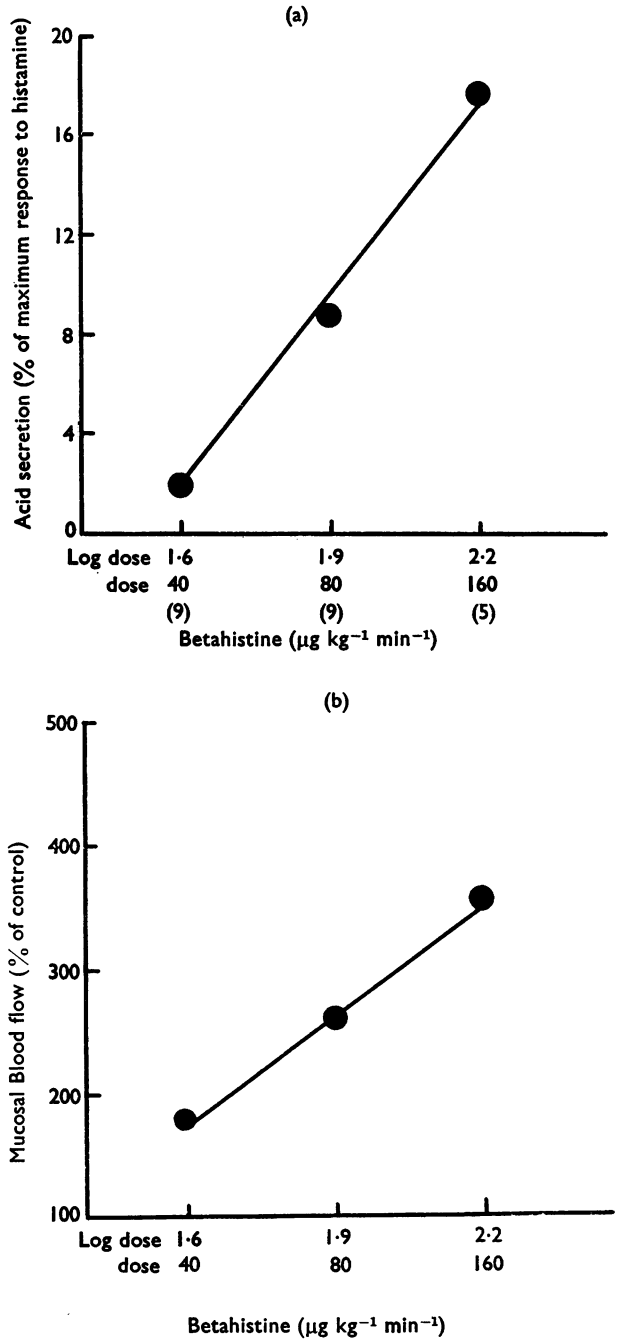

FIG. 1. The effect of betahistine on acid secretion and gastric mucosal blood flow in Heidenhain pouches, in three conscious dogs. (a) Ordinates: Acid secretion expressed as a percentage of the maximum response to histamine for these dogs. Abscissae: Dose of betahistine (log scale) μg kg^{-1} min^{-1}. The line is the calculated least squares regression line b=26 $P<0{\cdot}01$. The points are the mean results of the number of separate experiments (shown in parentheses). (b) Ordinates: Mucosal blood flow (measured as aniline clearance) expressed as percentage of blood flow during the control period. Abscissae: Dose of betahistine (log scale) μg kg^{-1} min^{-1}. The line is the calculated least squares regression line b=291 $P<0{\cdot}01$. The points are the mean results of 16 observations in 4 separate experiments.

the rate of acid secretion. However the larger doses (80 and 160 μg kg^{-1} min^{-1} i.v.) increased acid secretion by 8·8% and 17·6% respectively of the maximal response to histamine (Fig. 1a). There was no difference between the effects of betahistine given alone and on a background of secretion induced by a small dose of histamine or pentagastrin: the effect of betahistine was additive and there was no evidence of potentiation or inhibition of other stimuli.

Mucosal blood flow Betahistine (40–160 μg kg^{-1} min^{-1} i.v.) increased gastric mucosal blood flow at the three dose levels in each of four experiments as illustrated in Figure 1b.

Relative effects of betahistine on mucosal blood flow and secretion The ratio of mucosal blood flow to gastric secretion is given by the ratio of the concentrations of aniline in gastric juice and plasma. In these experiments the mean ratios ± S.E.M. for betahistine were 41·9 ± 6·2 (n=12) 42·5 ± 1·6 (n=24) and 149 ± 10·2 (n=12) in the three dogs compared with a mean ratio of 37·2 ± 3·4 (n=36) for histamine in the same dogs at comparable levels of secretion.

The effect of betahistine on pouch drainage In one of the dogs the pouch drained less well during the largest dose of betahistine so that the volume of secretion collected during the last 15 min of infusion was small. In the subsequent 15 min, after the infusion of betahistine had ceased, a large volume of secretion was collected. The collections from the two periods were combined in the results for acid secretion described above. This observation suggests that this dose of betahistine caused alterations in the muscle tone of the pouch so that the secretion did not drain out into the cannula. This effect was not so marked in the other two dogs.

Mucosal blood flow measurements were affected in a similar way in two of the dogs. The results shown in Fig. 1b, however, do not include the periods after infusion of betahistine. If they are included the mean percentage blood flow is 502 for the dose of 160 μg kg^{-1} min^{-1}.

The ratio of mucosal blood flow to secretion depends only on the ratio of aniline concentration and not on the volume of juice collected. Therefore it is not affected by alteration in pouch drainage.

Discussion.—These results show that, compared with histamine, betahistine has little activity in stimulating gastric acid secretion. In confirmation of previous work in dogs and man we observed no stimulation of secretion with doses up to 40 μg kg^{-1} min^{-1}. When larger doses of betahistine were used a small but significant secretion was observed.

The vasodilator effect of betahistine which is known in other vascular beds has been demonstrated in the gastric mucosa. This was an expected result because gastric mucosal blood flow and secretion are intimately linked. In every situation in which secretion is increased mucosal blood flow is also increased (Jacobson, Linford & Grossman, 1966). However, not all secretagogues affect mucosal blood flow and secretion to the same extent. For example, the ratio of mucosal blood flow to secretion is greater for histamine than for pentagastrin (Jacobson & Chang, 1969; Reed & Smy, 1971; Curwain, 1972b). It is therefore of interest to consider this ratio for betahistine. In none of the dogs was the ratio less for betahistine than for histamine. In one of the three dogs the ratio was more than three times that for histamine and this difference was highly significant (P<0·001). In the other two dogs the ratio was not significantly different from the ratio for histamine. We conclude that there is considerable individual variation in the relative sensitivity of gastric mucosal blood vessels and the secretory mechanism for betahistine and histamine. Since betahistine does not *decrease* the ratio of gastric mucosal blood flow to secretion, at least in dogs, dyspepsia cannot be attributed to relative mucosal ischaemia. The possibility that dyspepsia might be associated with disturbance of gastric motility needs to be considered. In our experiments there was indirect evidence that betahistine affected gastric muscular tone. The effect of betahistine on isolated stomach muscle has not been reported but on isolated intestine it has about 8% of the activity of histamine (Werle & Palm, 1953).

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