Antagonism of vasodepressor and gastric secretory responses to histamine by ranitidine and cimetidine in the anaesthetised dog

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The histamine H_2-receptor antagonist ranitidine (AH 19065) is a potent inhibitor of gastric acid secretion in the anaesthetised rat and conscious Heidenhain pouch dog (Bradshaw, Brittain, Clitherow, Daly, Jack, Price & Stables, 1979). We have now compared ranitidine and cimetidine as antagonists of the effects of histamine on blood pressure and gastric acid secretion in the anaesthetised dog.

Beagle dogs (7–10 kg), anaesthetised with intravenous thiopentone (25 mg/kg), chloralose (50 mg/kg) and urethane (500 mg/kg), were prepared for measurement of arterial blood pressure, heart rate and ECG (lead II). For gastric secretion experiments, a Gregory cannula was inserted in the stomach through an abdominal incision, the pylorus ligated and secretion stimulated by a continuous intravenous infusion of histamine (1 $\mu g\ kg^{-1}\ min^{-1}$). With the dog raised in a prone position, gastric acid secretion was collected by drainage, the volume measured and H^+ concentration determined by titration. Gastric acid output, blood pressure, heart rate and ECG were monitored following intravenous ranitidine or cimetidine, given either as a bolus dose or an infusion for 30 minutes. Both antagonists were tested over a range of doses using at least 3 dogs per dose level.

Intravenous bolus doses of ranitidine (0.01–0.10 mg/kg) and cimetidine (0.1–1.0 mg/kg) caused dose-related inhibitions of gastric acid secretion of 33–78% and 22–84% respectively. Antisecretory ED_{50} values (with 95% confidence limits) were 0.027 (0.010–0.049) mg/kg for ranitidine and 0.26 (0.18–0.38) mg/kg for cimetidine. Gastric secretion was also inhibited following intravenous infusion for 30 min of ranitidine (1–10 $\mu g\ kg^{-1}\ min^{-1}$) and cimetidine (3–30 $\mu g\ kg^{-1}\ min^{-1}$). ED_{50} values were 2.2 (1.1–3.3) $\mu g\ kg^{-1}\ min^{-1}$ and 9.2 (6.1–13.7) $\mu g\ kg^{-1}\ min^{-1}$ respectively. Neither ranitidine nor cimetidine caused any appreciable change in blood pressure, heart rate or ECG at doses up to 35–40 times greater than their respective antisecretory ED_{50} values.

In a separate series of 11 experiments, following the method of Parsons & Owen (1973), dose response curves were constructed to histamine (0.1–300 μg/kg i.v.) for falls in diastolic blood pressure. The H_1-receptor antagonist, mepyramine (1 mg/kg i.v.) was injected 10 min before repeating the doses of histamine, and ranitidine or cimetidine was administered by continuous i.v. infusion for 15 min before and during the injections of histamine.

Mepyramine displaced the vasodepressor dose-response curve to histamine to the right, and combination of mepyramine with ranitidine (1 to 100 $\mu g\ kg^{-1}\ min^{-1}$) or cimetidine (10 to 1000 $\mu g\ kg^{-1}\ min^{-1}$) caused further parallel, dose-dependent displacements to the right of these dose-response curves. The same effect has previously been reported for burimamide (Parsons & Owen, 1973).

Thus, in the anaesthetised dog, ranitidine and cimetidine both inhibited histamine-induced gastric secretion without causing overt cardio-vascular effects, and in combination with an H_1-antagonist, inhibited vasodepressor responses to histamine. Ranitidine was 4–10 times more active than cimetidine in these experiments.

References

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