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Ranitidine (AH 19065): a new potent, selective histamine H_2-receptor antagonist

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Until now, an imidazole or an equivalent heterocyclic moiety has been thought to be an important feature in potent H_2-antagonists (Ganellin, Durant & Emmett, 1976). The purpose of this communication is to describe an H_2-antagonist which lacks this feature and whose exceptional potency may result in clinical advantage. The substance is N-{2-[[[5-(dimethylaminomethyl)-2-furanyl]methyl]-thio]ethyl}-N'-methyl-2-nitro-1,1-ethenediamine (AH 19065).

The H_2-antagonist activity of AH 19065 was determined using the guinea-pig isolated right atrium preparation suspended in Krebs solution at 32°C and gassed with 95% O_2:5% CO_2. Cumulative dose-response curves for histamine-induced increases in atrial rate were determined before and in the presence of AH 19065 (3.2×10^{-7} M – 3.2×10^{-6} M) or cimetidine (1.2×10^{-6} M – 1.2×10^{-5} M). Each drug concentration was tested on at least 6 preparations. Both drugs were competitive antagonists as shown by the dose-related, parallel displacements of the histamine dose-response curves and by the slope of the regression of log (DR-1) against log drug concentration. The slope for AH 19065 was 0.99 (95% confidence limits 0.83 – 1.16) and for cimetidine was 1.05 (0.80 – 1.29), both values being not significantly different from unity. The pA_2 values for AH 19065 and cimetidine were 7.20 (7.01 – 7.45) and 6.55 (6.32 – 6.91) respectively. AH 19065 is therefore about 4 times more active than cimetidine in this test.

The H_2-antagonism of AH 19065 on the guinea-pig atrium is a selective effect because concentrations up to 0.96×10^{-4} M had no effect on β-adrenoceptor-mediated chronotropic responses to isoprenaline. On the guinea-pig isolated ileum preparation AH 19065, at concentrations up to 3.2×10^{-4} m, did not antagonise the actions of histamine or bethanechol, indicating that AH 19065 is devoid of significant H_1-antagonist or anticholinergic activity.

AH 19065 and cimetidine were compared as inhibitors of gastric acid secretion in the rat and dog. In the perfused stomach preparation of the anaesthetized rat (Parsons, 1969) AH 19065 (0.03 – 1.0 mg/kg i.v.) and cimetidine (0.3 – 3.0 mg/kg i.v.) produced dose-related inhibitions of histamine-induced secretion. AH 19065 was about 5 times more potent than cimetidine, the antisecretory ED_{50} values being 0.13 (0.08 – 0.22) mg/kg and 0.73 (0.45 – 1.06) mg/kg respectively.

When tested against histamine-induced secretion in 5 conscious dogs with Heidenhain pouches AH 19065 (0.03 – 0.30 mg/kg i.v.; 0.1 – 1.0 mg/kg orally) and cimetidine (0.1 – 1.0 mg/kg i.v.; 0.3 – 3.0 mg/kg orally) caused dose-related inhibitions of secretion. The onset and duration of action of the two drugs were similar but AH 19065 was about 4 times more active than cimetidine, the oral ED_{50} values being 0.23 (0.17 – 0.29) and 0.96 (0.80 – 1.15) mg/kg respectively.

Ranitidine (AH 19065) is a selective H_2-antagonist *in vitro* and a potent, orally active inhibitor of histamine-induced gastric acid secretion *in vivo*.

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