The pharmacology of cimetidine, a new histamine H_2-receptor antagonist

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Burimamide and metiamide which have been described previously (Black, Duncan, Durant, Ganellin & Parsons, 1972; Black, Duncan, Emmett, Ganellin, Hesselbo, Parsons & Wyllie, 1973) are histamine H_2-receptor antagonists. This communication describes some aspects of the pharmacology of cimetidine (N-cyano-N'-methyl-N''[2-(5-methyl-4-imidazolyl-methylthio)ethyl] guanidine; SK&F 92334), a new H_2-receptor antagonist. *In vitro* the compound antagonizes the actions of histamine on isolated guinea-pig atrium and isolated electrically-stimulated rat uterus with K_B values of 7.9×10^{-7}M and 8.1×10^{-7}M respectively, corresponding to pA_2 values of 6.1 on each tissue. At very high concentrations cimetidine antagonizes the actions of isoprenaline on atrium and uterus and the actions of histamine and carbachol on isolated guinea-pig ileum but the results are not consistent with competitive antagonism at β-adrenoceptors, histamine H_1-receptors or muscarinic receptors.

The effects of cimetidine on gastric acid secretion have been studied in a number of preparations. The results are summarized in Table 1. In all preparations cimetidine was approximately equiactive in inhibiting histamine- and pentagastrin-stimulated acid secretion but less effective in inhibiting carbachol-stimulated secretion. Basal secretion was also inhibited. In Heidenhain pouch dogs the blood levels to give 50% inhibition of maximally-stimulated gastric secretion (EC50) were approximately 1-2 μM and the half-life of the compound about one hour.

In male human volunteers cimetidine given intravenously has been shown to inhibit histamine- or pentagastrin-stimulated gastric secretion with an EC50 of about 2.5 μM and a half-life of about two hours.

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TABLE 1 The effects of cimetidine on gastric acid secretion

Preparation	*Stimulant*	*Effect of Cimetidine*
Rat: Lumen-perfused stomach	Histamine 15 μmol kg^{-1} h^{-1}	ID50 (rapid i.v. injection) 1.37 μmol/kg ID50 (intraduodenal administration) 5.5 μmol/kg i.v. infusion of 3 μmol kg^{-1} h^{-1} produced mean inhibition of 71%
	Pentagastrin 60 μg kg^{-1} h^{-1}	ID 50 (rapid i.v. injection) 1.4 μmol/kg
	Carbachol 30 μg kg^{-1} h^{-1}	Variable effect. Significant inhibition at 8 μmol/kg Approximately 50% inhibition at 128-256 μmol/kg
Rat: Gastric fistula	Basal secretion	i.v. infusion of 6 μmol kg^{-1} h^{-1} produced mean inhibition of 20% in first hour and 30% in second hour. With 60 μmol kg^{-1} h^{-1} inhibitions were 71% and 96% respectively.
Cat: Lumen-perfused stomach	Histamine 3 μmol kg^{-1} h^{-1} Pentagastrin 10 μg kg^{-1} h^{-1}	ID50 (rapid i.v. injection) 0.85 μmol/kg ID50 (rapid i.v. injection) 1.45 μmol/kg
Dog: Heidenhain pouch	Histamine 1.3 μmol kg^{-1} h^{-1}	ID50 (rapid i.v. injection) 1.7 μmol/kg ID50 (i.v. infusion) 4.7 μmol kg^{-1} h^{-1} Oral administration of 10 & 20 μmol/kg produced mean inhibitions of 70 & 90% respectively
Dog: Heidenhain pouch	Pentagrastrin 8 μg kg^{-1} h^{-1}	2 μmol/kg by rapid i.v. injection gave mean inhibition of 55%
	Carbachol 6.7 μg kg^{-1} h^{-1}	4 μmol/kg by rapid i.v. injection gave mean inhibition of 59%

In chronic toxicity studies metiamide has been shown at high doses to produce kidney damage and agranulocytosis in some dogs (Brimblecombe, Duncan & Walker, 1973). In tests so far carried out cimetidine at equivalent doses has not shown similar toxicity.

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Observations on the effect of dibenzoxazepine (CR) and N-nonoyl-vanillylamide (VAN) on sensory nerves

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VAN and CR cause a burning pain when applied to the human skin (Ballantyne, Beswick & Price-Thomas, 1973). This action has been investigated in cats by the application to a burn blister and to intact skin on the hindleg. Recordings were made from the sensory nerves innervating these areas.

Cats were anaesthetized with α-chloralose 70-90 mg/kg, and the blood pressure was monitored. The saphenous nerve was exposed in the thigh. The nerve was immersed in liquid paraffin and prepared for multifibre and single unit recording (Iggo, 1960). Nerve activity was recorded by bipolar silver electrodes, displayed on an oscilloscope for photography and stored on magnetic tape for further analysis using a small computer. Sensory units were identified by their response to mechanical stimulation of the skin, and by the conduction velocity and/or duration of the action potential in the related nerve fibres. Burn blisters were prepared by placing a metal disc (2 cm) at 100°C on the skin for 10 seconds. Close-i.a. injection of drugs employed the saphenous artery.

Only in four out of ten experiments where a blister had been prepared were the nerves innervating the blister identified. Isotonic KCl was applied in all four experiments to the blister base and found to cause activity in the isolated nerve fibres. Onset of action varied between 5 s and 1 min 45 seconds. On application of CR or VAN 10^{-4} M in saline no effects attributed to the drugs were observed. To test whether the preparations had been desensitized isotonic KCl was added again and was found to be effective in all cases.

Application of CR 10^{-4} M to intact skin. In six out of twenty-one preparations C-fibre units were isolated. These fine strands of nerves also contained in most cases alpha mechanoreceptors which were of low threshold and failed to respond. Five of these C-fibre units responded to CR and comprised 2 moderate threshold mechnoreceptors, 1 high threshold mechanoreceptor, 1 thermoreceptor and 1 unidentified receptor unit. Onset of activity in these units ranged between 5-8 min except for high threshold unit where the skin area was broken and activity occurred in 5 seconds. All these units showed immediate tachyphylaxis but still responded to physical stimulation. In some of these units, especially the thermoreceptor, saline was applied to the skin 45 min after CR response had subsided. Activity occurred within 5 min 5 seconds. This could be related to a similar phenomenon observed on human skin (Ballantyne, Beswick & Price-Thomas, 1973). All fibres affected by CR responded to 30 μg 5-HT and to 30 μg bradykinin injected close-i.a. Both compounds showed tachyphylaxis, but 5-HT more readily. Only some α fibres were affected by these compounds, probably the slowly adapting units (Fjallbrant & Iggo, 1961; Beck & Handwerker, 1974).

The observations suggest that CR acts on specific sensory units related to unmyelinated fibres. Research is continuing to clarify if the effect is indirect or direct and rigidly classify the fibre units which these compounds excite.

We wish to thank Professor A. Iggo for very helpful discussions and for demonstrating the technique.