What is New in Veterinary Clinical Pharmacology?

Cimetidine and Ranitidine, Histamine-H_2 Receptor Antagonists: Potential Veterinary Therapeutic Uses?

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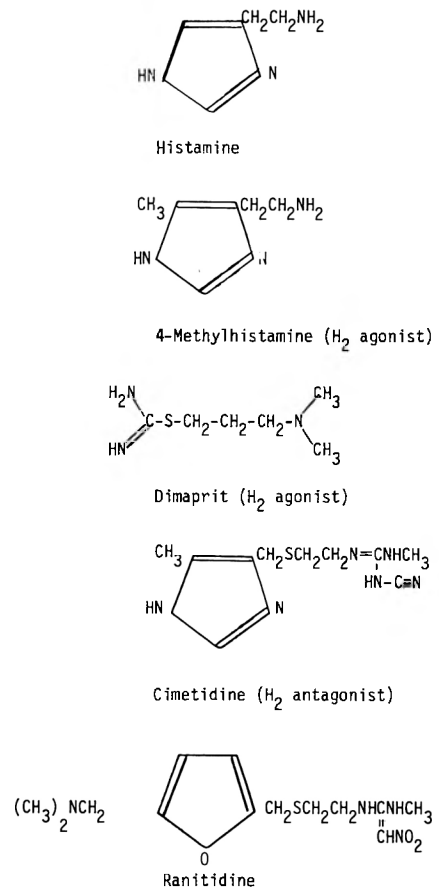
Chemistry and Source: Histamine-H_2 receptor antagonists were developed by the intentional modification of the histamine formula in the search for chemically related compounds that would act as competitive inhibitors of the H_2 receptors. (Hirschowitz, 1979). Cimetidine (N"-cyano-N-methyl-N'-[2-[[(5-methyl-1 H-imidazole-4-yl) methyl] thio]-ethyl]-guanide is one of the imidazole histamine H_2 antagonists whereas Ranitidine (N[2-[[[5-[(dimethyl-amino) methyl]-2-furanyl] methyl] thio] ethyl]-N-methyl-2-nitro-1, 1-ethenediamine is a non-imidazole, (but substituted amino-alkyl-furan derivative of histamine) histamine-H_2 antagonist. (Figure 1). Both Cimetidine hydrochloride (Tagamet®-SK and F Co.) and Ranitidine hydrochloride (Zantac®-Glaxo Inc.) approved by the Food and Drug Administration for medical use are commercially available.

Figure 1. Chemical structures of Histamine, H_2-receptor agonists and antagonists.



Histamine-H_1 and H_2 Receptors: Histamine, 2-(4-imidazolyl) ethylamine or β-aminoethyl imidazole is one of the endogenous biogenic monoamines, produced as a result of decarboxylation of the amino acid, histidine. It is widely distributed throughout mammalian tissue but its amount and storage sites within the mammalian body vary considerably in different species. Endogenously synthesized histamine is stored in both the mast cell pool including mast cells and basophils (eosinophils in dogs) and the non-mast cell pool including the epithelial cells of the natural body orifices (gastrointestinal tract, respiratory tract, genito-urinary tract) and the skin that are exposed to the amosphere and the central nervous system. Endogenously stored histamine is known to be released by physical, (mechanical trauma; cold and heat; ultraviolet radiation), chemical (drugs, including antibiotics, alkaloids, sympathomimetic amines, dextran, polyvinylpyrrolidine, 48/80) and biological (toxins, venoms, proteolytic enzymes, antibody-antigen reaction) "stressors." This monoamine is known to play a vital role in the health and disease of both animals and humans. Histamine either endogenously released in response to "stressors" or exogenously administered is currently known to produce it various physiological or pharmacological effects by directly binding with H_1 and H_2 type receptors of various target organs of both animals and humans. (Table 1).

Histamine-H_2 Receptors and Gastric Acid Secretion: Histamine is ubiquitously distributed in the animal

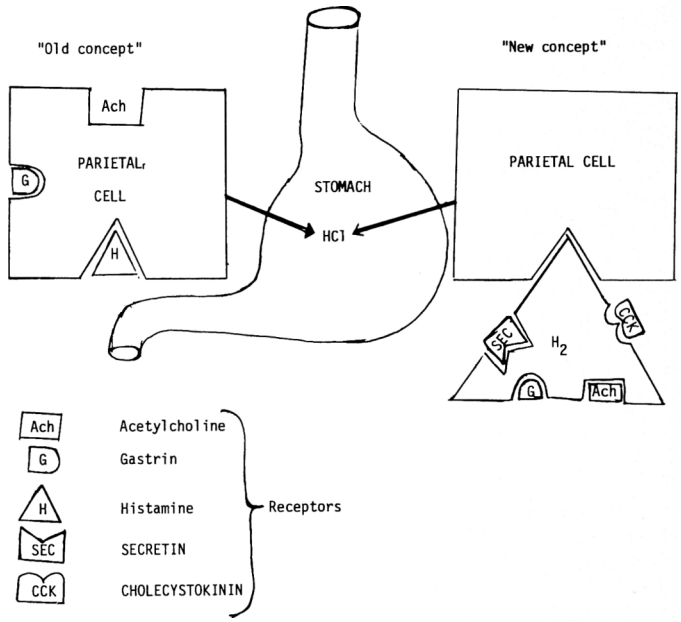
TABLE 1. Types of Histaminergic Receptors and Responses

Type	Target Organs	Physiological/ Pharmacological Responses	Specific Agonists	Specific Antagonists
H_1	Smooth muscles of Bronchi and Gut Lacrimal Salivary Bronchial Pancreatic Intestinal glands	Contraction Hypersecretion	Histamine, 2-methyl Histamine	Pyrilamine, Mepyramine, etc., the classical antihistamines (H_1 antagonists)
H_2	Gastric Glands - parietal cells Heart	Hypersecretion Positive chrono and inotropic effects	Betazole, Histamine 4-methyl Histamine	Cimetidine, Ranitidine. (H_2 antagonists)
H_1 & H_2 (Mixed)	Fine Blood Vessels CNS	Vasodilation, Increased Capillary permeability Hypotension Behavioral Responses	Histamine	Both H_1 & H_2 antagonists

kingdom, being present in all chordates except the stomachless carp. Though there is great variability in histamine content from tissue to tissue, only the gastric mucosa of all vertebrates is relatively rich in histamine, that is, there is a selective accumulation of histamine related to acid secretory cells. Although many aspects of mechanism(s) as well as physiologic control of gastric acid secretion remain unknown, gastric secretion is strongly stimulated by histamine in all vertebrates investigated. According to the old school of thought, there are specific receptor sites for acetylcholine, gastrin and histamine respectively at parietal cells of gastric mucosa and the secretion of acid by the stomach depends on the binding of acetylcholine, gastrin and histamine to their respective receptors on the parietal cell surface (Figure 2). The current school of thought is that Histamine-H_2 receptor on the parietal cell is a major controller of the acid production and is the final common path to the parietal cell (Figure 2; Code, 1977). Histamine thus seems to serve a specific function relative to acid secretion. The failure to inhibit histamine induced gastric acid secretion by H_1 antagonists, such as mepyramine, the classical antihistamine defined the effect as H_2. This has been amply confirmed by the use of H_1 and H_2 receptor specific agonists and antagonists (Table 1).

Pharmacologic Properties of Cimetidine and Ranitidine: Gastric secretion—Both cimetidine and ranitidine have been shown both in animals and man to inhibit basal acid secretions and secretion stimulated by pentagastrin, histamine, betha nechol, sham feeding and real feeding. On a molar basis, ranitidine is 4 to 13 times more potent than cimetidine in inhibiting stimulated gastric acid secretion in human subjects. Both cimetidine and ranitidine decrease gastric blood flow and the volume of gastric secretion. There is also a decrease in pepsin output; however, this appears to be secondary to the reduced volume of gastric secretion, since the pepsin concentration in the gastric juice remains unchanged. Both cimetidine and ranitidine appear to have little or no effect on gastric motility, gastrin production or pancreatic enzyme output (Zeldis *et al.,* 1983, Helman and Tim, 1983).

Figure 2: Mechanisms(s) of Gastric Acid Secretion.



Endocrine Effects: While therapeutic doses of cimetidine have been shown to elevate plasma prolactin levels and be antiandrogenic leading to gynaecomastia, galactorrhoea in female and sexual dysfunction in males respectively, ranitidine appears to have minimal effects on endocrine functions (Helman and Tim, 1983).

Hepatic Drug Metabolism: Cimetidine, but not ranitidine, has been demonstrated to inhibit hepatic microsomal drug metabolism enzymes leading to an alteration of pharmacokinetics (elimination) of those drugs metabolized by hepatic microsomal monoxygenases both in animals and humans (Mangini, 1982).

Human Clinical Pharmacology: Pharmacokinetics —Both cimetidine and ranitidine are well absorbed (70% and 50% respectively) following their oral administration. At therapeutic doses of 150 mg every 12 hrs., ranitidine reduces 24-hour gastric acidity by 69% compared with cimetidine, 200 mg three times daily before meals and 400 mg at bedtime, which reduces 24-hour acidity by 48% and nocturnal acidity by 70%. The serum half-life of orally administered cimetidine and ranitidine is approximately 2-3 hours. While most of an oral dose of cimetidine is excreted unchanged in the urine within 24 hours, the bioavailability of ranitidine is influenced by hepatic function, since the drug is taken up and metabolized by the liver by "first pass" kinetics. Up to 30% is metabolized by the liver but 50% or more of the drug is excreted by the kidney unchanged. In geriatric patients, the half-life of ranitidine is prolonged by about 50% presumably because of a decrease in the glomerular filtration rate. As expected, the bioavailability of ranitidine in patients with liver disease is increased, and the serum half-life is slightly prolonged because of decreased hepatic metabolism and a slightly reduced glomerular filtration rate (Young *et al.,* 1982).

Clinical Uses: Following is the partial list of clinical uses of cimetidine and ranitidine in humans.

1. Duodenal ulcer
2. Hypersecretory states
   a. Zollinger-Ellison Syndrome (Gastrin excess)
   b. Systemic mastocytosis or basophil leukemia (histamine excess)
3. Gastric ulcer
4. Reflux esophagitis — gastrointestinal bleeding
5. Acute erosive gastritis
6. Stress-induced gastritis (anesthesia, surgery, etc.)

Dosage Forms:

Cimetidine — (Tagamet®)

Tablets: Each tablet contains 200 mg or 300 mg of cimetidine

Liquid: Each 5 ml contains in aqueous solution, cimetidine hydrochloride equivalent to cimetidine 300 mg. Vials (2 & 8 ml): Each 2 ml contains in aqueous solution cimetidine hydrochloride equivalent to cimetidine 300 mg.

Ranitidine — (Zantac®)

Tablets — Each tablet contains 168 mg of ranitidine hydrochloride, equivalent to 150 mg ranitidine.

Potential Veterinary Clinical Uses:

Although pharmacodynamic and pharmacokinetic data from well controlled veterinary clinical pharmacological studies are not available at present, the practicing veterinarians can use both cimetidine and ranitidine for the following clinical conditions listed in Table 2.

TABLE 2. Some of the Potential Veterinary Clinical Uses of Cimetidine (Tagamet®) and Ranitidine (Zantac®)

1. Esophageal gastric ulcers in pigs
2. Gastrointestinal ulcers in foals
3. Abomasal ulcers in calves, cattle
4. Abomasal ulcers in lambs
5. Gastric ulcers (uremic) in dogs
6. Duodenal ulcers in dogs
7. Hemorrhagic gastritis in dogs
8. Reflux esophagitis in dogs

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