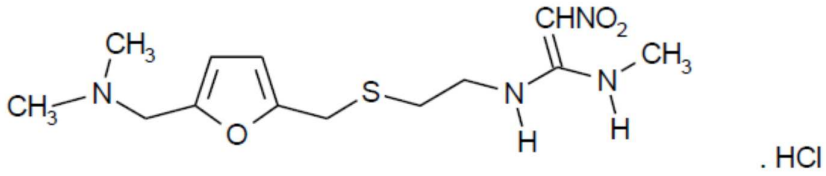
NEW ZEALAND DATA SHEET

RANITIDINE RELIEF

Ranitidine film coated tablets, 150 mg and 300 mg

Name of the drug

Ranitidine (as hydrochloride). The chemical name for ranitidine hydrochloride is N-[2-[[[5-[(dimethylamino)methyl]-2-furan-yl]methyl]thio]ethyl]-N'-methyl-2-nitro-1,1-ethenediamine hydrochloride. Its structural formula is:



$C_{13}H_{22}N_4O_3S.HCl$ Molecular weight: 350.9 CAS No.: 66357-59-3

Description

Ranitidine hydrochloride is a white or pale yellow crystalline powder with a slightly bitter taste and sulfur-like odour. It is an aminoalkyl substituted furan and is structurally different from cimetidine, lacking the imidazole ring and the cyanoguanidine group. Ranitidine hydrochloride is freely soluble in water and methanol and sparingly soluble in ethanol (96%).

Ranitidine Relief tablets come in two strengths and contain either 150 mg or 300 mg of ranitidine (as hydrochloride). The tablets also contain the following excipients: magnesium stearate, microcrystalline cellulose, colloidal anhydrous silica, croscarmellose sodium, purified talc, isopropyl alcohol, yellow iron oxide, titanium dioxide, castor oil and hypromellose. The tablets are gluten and lactose free.

Pharmacology

Animal experiments both *in vitro* and *in vivo* have established that ranitidine is a selective, competitive antagonist of histamine at H_2-receptor sites. Ranitidine has no significant interaction at histamine H_1-receptors, muscarinic receptors or beta-adrenoreceptors. Ranitidine is a potent inhibitor of gastric secretion in the rat and dog.

All the evidence from human studies is compatible with a selective, competitive antagonism of histamine H_2-receptors by ranitidine in humans. Oral or intravenous administration of ranitidine inhibits both basal gastric secretions and gastric acid secretion induced by histamine, pentagastrin and other secretagogues. On a weight basis ranitidine is between four and nine times more potent than cimetidine.

After oral administration of ranitidine, the plasma concentrations of ranitidine achieved are directly related to the dose administered. A plasma ranitidine concentration of 50 to 100 nanogram/mL has an inhibitory effect upon stimulated gastric acid secretion of approximately 50%.

Inhibition of pentagastrin-induced gastric acid secretion increases with dose, being approximately 90% two hours after an oral 150 mg dose and a significant effect is still evident 12 hours after this dose. In ten patients with duodenal ulcer, ranitidine 150 mg given orally every 12 hours significantly reduced mean 24 hour hydrogen ion activity by 69% and nocturnal gastric acid output by 90%,

whereas cimetidine (200 mg three times daily and 400 mg at night) reduced mean 24 hour hydrogen ion activity by 48% and nocturnal gastric acid output by 70%.

Pepsin secretion is also inhibited by ranitidine, but secretion of gastric mucus is not affected. Ranitidine does not alter the secretion of bicarbonate or enzymes from the pancreas in response to secretin and pancreozymin.

Reduction in gastric acid secretion induced by ranitidine 150 mg twice daily for seven days did not cause bacterial overgrowth in the stomach.

Pulse rate, blood pressure, ECG and EEG were not significantly affected in humans following recommended doses of ranitidine.

Chronic ranitidine therapy (300 mg/day for 28 days) had no effect on serum prolactin, gastrin, thyroid stimulating hormone, follicle stimulating hormone, luteinising hormone, gonadotrophins, testosterone, oestriol, progesterone or cortisol levels.

One study in 30 male patients with duodenal ulcer showed a significant decrease in basal thyroxine levels after four weeks of treatment with ranitidine 300 mg daily, but no significant change in thyroid stimulating hormone was noted. Acute administration of ranitidine 50 mg intravenously had no effect on plasma aldosterone in healthy male volunteers whereas it caused a significant reduction in vasopressin. Cimetidine 200 mg intravenously had a similar effect on vasopressin.

Pharmacokinetics

Absorption

Peak plasma levels occur about two to three hours after oral administration of ranitidine. Absorption is not significantly altered by food or concurrent antacid administration.

Following oral administration of 150 mg ranitidine, maximum plasma concentrations (300 to 580 nanogram/mL) occurred after 1 to 3 hours. Two distinct peaks or a plateau in the absorption phase suggest reabsorption of drug secreted into the intestine. The absolute bioavailability of ranitidine is 50 to 60%, and plasma concentrations increase proportionally with increasing dose up to 200 mg. Bioavailability of ranitidine is approximately 50%. Serum protein binding of ranitidine in humans is in the range 10 to 19%. The elimination half-life is approximately two hours.

Distribution

Ranitidine is not extensively bound to plasma proteins (15%), but exhibits a large volume of distribution ranging from 96 to 142 L.

Metabolism

The fraction of the dose recovered as metabolites is similar after both oral and intravenous dosing; and includes 6% of the dose in urine as the N-oxide, 2% as the S-oxide and small amounts of desmethylranitidine and the furoic acid analogue. The 24 hour urinary recovery of free ranitidine and its metabolites is about 40% after oral administration of the drug.

Excretion

Plasma concentrations decline bi-exponentially, with a terminal half-life of 2 to 3 hours. The major route of elimination of unchanged asenapine is renal. Renal clearance is approximately 500 mL/min, which exceeds glomerular filtration indicating net renal tubular secretion.

Patients over 50 years of age:

In patients over 50 years of age, half-life is prolonged (3 to 4 hours) and clearance is reduced, consistent with the age-related decline of renal function. However, systemic exposure and accumulation are 50% higher. This difference exceeds the effect of declining renal function, and indicates increased bioavailability in older patients.

Impairment of renal function requires a reduction in dosage (see Precautions). Impairment of liver function may increase the bioavailability of ranitidine but has no significant effect on the elimination half-life. However, in the presence of normal renal function, no dosage reduction for ranitidine appears necessary in patients with hepatic impairment.

Indications

Rantidine Relief is indicated for the treatment of duodenal ulcer and benign gastric ulcer.

The pathogenesis of duodenal ulcer disease is multifactorial and infection with *Helicobacter pylori* appears to be one important factor in the process. The United States National Institute of Health has recommended that regimens to eradicate *Helicobacter pylori* in patients with peptic ulcer disease, whether on first presentation with the illness or on recurrence, should contain both anti-secretory agents (including H_2-antagonists) and anti-microbial agents (to which *Helicobacter pylori* has been demonstrated to be sensitive *in vivo*). A trial in patients with recurrent duodenal ulcer disease demonstrated that ranitidine in combination with amoxicillin (750 mg three times daily) and metronidazole (500 mg three times daily) for 12 days is effective in eradicating *Helicobacter pylori* in 89% of cases. Following this combination therapy the relapse rate for duodenal ulcer disease was only 2% at 12 months suggesting a causal role for *Helicobacter pylori* in recurrent duodenal ulcer. Therefore ranitidine, when used in a treatment regimen with amoxicillin and metronidazole, is indicated for the treatment of duodenal ulcers associated with *Helicobacter pylori* infection.

Ranitidine Relief is also indicated for:

- the treatment of duodenal ulcer and benign gastric ulcer associated with non-steroidal anti-inflammatory agents.
- the prevention of non-steroidal anti-inflammatory agent (including aspirin) associated duodenal ulcers in patients with a history of duodenal ulceration proven by endoscopy.
- the treatment of post-operative ulcer
- the treatment of chronic episodic dyspepsia, characterised by pain (epigastric or retrosternal) which is related to meals or disturbs sleep but not associated with the above conditions.
- symptom relief in gastro-oesophageal reflux disease
- the treatment of oesophageal reflux disease
- the treatment of Zollinger-Ellison syndrome

Ranitidine Relief is also indicated for the following conditions where reduction of gastric secretion and acid output is desirable:

- the prophylaxis of upper gastrointestinal haemorrhage from stress ulceration in seriously ill patients.
- the prophylaxis of recurrent haemorrhage in patients with bleeding peptic ulcers.
- before general anaesthesia in patients considered to be at risk of acid aspiration (Mendelson's syndrome), particularly obstetric patients during labour.

Pharmacy-Only and General Sale Indication

Ranitidine Relief is indicated for the symptomatic relief of heartburn, dyspepsia and hyperacidity in adults and children over 12 years.

Contraindications

Patients with known hypersensitivity to ranitidine hydrochloride or to any component of this product.

Precautions

Gastric ulcer: Treatment with a histamine H_2-antagonist may mask symptoms associated with carcinoma of the stomach and therefore may delay diagnosis of the condition. Accordingly, where gastric ulcer is suspected, the possibility of malignancy should be excluded before therapy is instituted.

Long-term use: The risk of ulcer recurrence is determined by many factors. In some cases, long periods of treatment may be necessary and/or repeated. Evidence from controlled clinical trials of up to 18 months continuous treatment with ranitidine has not revealed any undue untoward effects.

Porphyria: Rare clinical reports suggest that ranitidine may precipitate acute porphyric attacks. Ranitidine should therefore be avoided in patients with a history of acute porphyria.

Gastric pH: Agents that elevate gastric pH may increase the already present risk of nosocomial pneumonia in intubated ICU patients receiving mechanical ventilation.

Impaired renal function: Ranitidine is excreted via the kidneys and in the presence of severe renal impairment plasma levels of ranitidine are increased and prolonged. Accordingly, in the presence of significant renal impairment, serum levels should be monitored and dosage adjustments made. The clearance of ranitidine is increased during haemodialysis.

Effects on fertility: There are no data on the effects of ranitidine on human fertility. Reproduction studies performed in rats and rabbits have revealed no evidence of impaired fertility or harm to the foetus due to ranitidine.

Use in pregnancy (Category B1): The safety of ranitidine in pregnancy has not been established. Ranitidine crosses the placenta. Ranitidine should only be used during pregnancy if considered essential. If the administration of ranitidine is considered to be necessary, its use requires that the potential benefits be weighed against possible hazards to the patient and to the foetus.

Use in lactation: Ranitidine is secreted in breast milk in lactating mothers, but the clinical significance of this has not been fully evaluated. Ranitidine should only be used by nursing mothers if considered essential.

Use in children: Experience with ranitidine tablets in children is limited and such use has not been fully evaluated in clinical studies. It has however been used successfully in children aged 8 to 18 years in doses up to 150 mg twice daily.

In patients such as the elderly, persons with chronic lung disease, diabetes or the immunocompromised, there may be an increased risk of developing community acquired pneumonia. A large epidemiological study showed an increased risk of developing community acquired pneumonia in current users of H_2-receptor antagonists versus those who had stopped treatment, with an observed adjusted relative risk of 1.63 (95% CI, 1.07-2.48).

Interactions

Ranitidine has the potential to affect the absorption, metabolism or renal excretion of other drugs. The altered pharmacokinetics may necessitate dosage adjustment of the affected drug or discontinuation of treatment.

Interactions occur by several mechanisms including:

1) Inhibition of cytochrome P450-linked mixed function oxygenase system:
Ranitidine at usual therapeutic doses does not potentiate the actions of drugs which are inactivated by this enzyme system such as diazepam, lidocaine, phenytoin, propranolol and theophylline.

There have been reports of altered prothrombin time with coumarin anticoagulants (e.g. warfarin). Due to the narrow therapeutic index, close monitoring of increased or decreased prothrombin time is recommended during concurrent treatment with ranitidine.

2) Competition for renal tubular secretion:
Since ranitidine is partially eliminated by the cationic system, it may affect the clearance of other drugs eliminated by this route. High doses of ranitidine (e.g. such as those used in the treatment of Zollinger-Ellison syndrome) may reduce the excretion of procainamide and N-acetylprocainamide resulting in increased plasma levels of these drugs.

3) Alteration of gastric pH:
The bioavailability of certain drugs may be affected. This can result in either an increase in absorption (e.g. triazolam, midazolam, glipizide) or a decrease in absorption (e.g. ketoconazole, atazanavir, delaviridine, gefitnib).

If high doses (2 g) of sucralfate are co-administered with ranitidine the absorption of the latter may be reduced. This effect is not seen if sucralfate is taken after an interval of two hours.

Adverse Reactions

The following have been reported as events in clinical trials or in the routine management of patients treated with ranitidine. The relationship to ranitidine therapy has not been clear in many cases. Headache, sometimes severe, has been reported in a very small proportion of patients.

Central nervous system: Rarely, malaise, dizziness, somnolence, insomnia and vertigo. Rare cases of reversible mental confusion, depression and hallucinations have been reported, predominantly in severely ill and elderly patients. In addition reversible involuntary movement disorders have been reported rarely. There have been a few reports of reversible blurred vision suggestive of a change in accommodation. Reversible impotence has been reported rarely.

Cardiovascular: As with other H_2-receptor antagonists, rare reports of tachycardia, bradycardia, premature ventricular beats, A-V block and asystole.

Gastrointestinal: Constipation, diarrhoea, nausea/ vomiting, abdominal discomfort/ pain.

Hepatic: Transient and reversible changes in liver-function tests can occur. There have been occasional reports of hepatitis, hepatocellular or hepatocanalicular or mixed, with or without jaundice. These were usually reversible.

Musculoskeletal: Rare reports of arthralgias and myalgia.

Haematological: Rare reports of agranulocytosis or pancytopenia, sometimes with marrow hypoplasia or aplasia, have been reported. Blood count changes (leucopenia, thrombocytopenia) have occurred in a few patients. These are usually reversible.

Endocrine: Controlled studies in animals and humans have shown no stimulation of any pituitary hormone by ranitidine, no anti-androgenic activity, and cimetidine-induced gynaecomastia and impotence in hypersecretory patients have resolved when ranitidine was substituted. However, occasional cases of breast conditions such as gynaecomastia and galactorrhoea, impotence and loss of libido have been reported in male patients receiving ranitidine but the incidence did not differ from that in the general population.

Dermatological: Rash including rare cases of mild erythema multiforme. Rare cases of vasculitis and alopecia have been reported.

Renal: Very rare cases of acute interstitial nephritis have been reported.

Other. Rare cases of hypersensitivity reactions (e.g. fever, bronchospasm, anaphylactic shock, urticaria, angioneurotic oedema, hypotension, chest pain, rash, eosinophilia), small increases in serum creatinine. Acute pancreatitis has been reported rarely.

Dosage and Administration

Duodenal or gastric ulceration

Acute treatment: 300 mg taken as a single dose at bedtime, or 150 mg taken twice daily, in the morning and at bedtime.

It is not necessary to time the dose in relation to meals. In most cases healing will occur in four weeks although a small number of patients may require an additional two to four weeks therapy.

Maintenance treatment: Duodenal ulcer. 150 mg taken at night.

As smoking is associated with a higher rate of ulcer relapse, patients should be advised to stop smoking. In patients unable to stop smoking, a dose of 300 mg at night provides additional therapeutic benefit.

Gastric ulcer

150 mg taken at night for a period of one year.

Gastrinoma (Zollinger-Ellison syndrome)

150 mg taken three times daily initially and increased, as necessary, to 600 to 900 mg/day.

Oesophagitis

300 mg taken as a single dose at bedtime or 150 mg taken twice daily, in the morning and at bedtime. It is not necessary to time the dose in relation to meals. In severe reflux oesophagitis the efficacy of 300 mg, taken as a single dose at bedtime, has been established for treatment periods of up to three months.

Maintenance treatment for reflux oesophagitis. 150 mg taken twice daily in the morning and at bedtime.

Acute symptomatic relief of heartburn, dyspepsia and hyperacidity

Take one 300 mg tablet at the first sign of any symptoms. Do not exceed one tablet in 24 hours.

or

Take one 150 mg tablet at the first sign of any symptoms. Repeat the dose if the symptoms return. Do not exceed two tablets in 24 hours.

Overdosage

There has been limited experience of overdosage with oral doses of ranitidine. Reported acute ingestions of up to 18 g orally have been associated with transient adverse effects similar to those encountered in normal clinical experience. (See Adverse Reactions.) Symptomatic and supportive therapy should be given as appropriate. If need be, the drug may be removed from the plasma by haemodialysis.

For further advice on management of overdose please contact the National Poisons Information Centre (0800 POISON or 0800 764 766).

Presentation

Ranitidine Relief 150mg tablet: a creamy-yellow, round, biconvex film coated tablet marked R150 on one side. Supplied in blister packs of 10, 20, 250 or 500 tablets.

Ranitidine Relief 300mg tablet: a creamy-yellow, round, biconvex film coated tablet marked R300 on one side. Supplied in blister packs of 10, 250 or 500 tablets.

Not all pack sizes may be marketed.

Storage

Store below 25℃.

Medicines Classification

General Sale Medicine: 150 mg blister pack of 10 tablets

Pharmacy Only Medicine: 150 mg blister pack of 20 tablets and 300 mg blister pack of 10 tablets

Prescription Only Medicine: Blister pack of 250 and 500 tablets

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