PRODUCT MONOGRAPH

ratio*-RANITIDINE

(ranitidine hydrochloride tablets, BP)

150 mg & 300 mg

Histamine H_2 receptor antagonist

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Control# 087630

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ACTION AND CLINICAL PHARMACOLOGY

Ranitidine is an antagonist of histamine at gastric H_2 receptor sites. Thus ranitidine inhibits both basal gastric secretion and gastric acid secretion induced by histamine, pentagastrin and other secretagogues. On a weight basis, ranitidine is between 4 and 9 times more potent than cimetidine. Inhibition of gastric acid secretion has been observed following intravenous, intraduodenal and oral administration of ranitidine. This response is dose related, a maximum response being achieved at an oral dose of 300 mg/day.

Pepsin secretion is also inhibited 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.

Ranitidine is rapidly absorbed after oral administration, peak plasma concentrations being achieved within 2 to 3 hours. These plasma concentrations are not significantly influenced by the presence of food in the stomach at the time of the oral administration nor by regular doses of antacids.

Bioavailability of oral ranitidine is approximately 50%. Serum protein binding of ranitidine in man is in the range of 10 to 19%. The elimination half-life is approximately 3 hours. The principal route of excretion is the urine (40% recovery of free and metabolized drug in 24 hours).

There is a significant linear correlation between the dose administered and the inhibitory effect upon gastric acid secretion for oral doses up to 300 mg. A plasma ranitidine concentration of 50 ng/mL has an inhibitory effect upon stimulated gastric acid secretion of approximately 50%. Estimates of the IC_{50} range from 36 to 94 ng/mL. Following the administration of 150 mg ranitidine orally, plasma concentrations in excess of this lasted for more than 8 hours and after 12 hours the plasma concentrations were sufficiently high to have a significant inhibitory effect upon gastric acid secretion. In patients with duodenal ulcer, 150 mg oral ranitidine every 12 hours significantly reduced mean 24-hour hydrogen ion activity by 69% and nocturnal gastric acid output by 90%. Furthermore, 300 mg oral ranitidine given at night is as effective in reducing 24-hour intragastric acidity as 150 mg ranitidine given orally twice daily.

Tablets:
In respect of both 24 hours acidity and nocturnal acid output, an oral dose of ranitidine

150 mg twice daily was superior to cimetidine 200 mg 3 times daily and 400 mg at night ($p<0.001$ and $p<0.05$ respectively).

Treatment of volunteers with oral ranitidine 150 mg twice daily for 7 days did not cause bacterial overgrowth in the stomach.

Volunteers treated with an oral dose of ranitidine have reported no significant gastrointestinal or CNS side effects; moreover pulse rate, blood pressure, ECG and electroencephalogram were not significantly affected in man following ranitidine administration.

In healthy human volunteers and patients, ranitidine when administered orally, did not influence plasma levels of the following hormones - cortisol, testosterone, oestrogens, growth hormone, follicle stimulating hormone, luteinizing hormone, thyroid stimulating hormone, aldosterone or gastrin - although like cimetidine, ranitidine reduced vasopressin output. Treatment for up to 6 weeks with ranitidine 150 mg twice daily by mouth did not affect the human hypothalamic-pituitary-testicular-ovarian or -adrenal axes.

A randomized, 2-way crossover study was conducted in healthy volunteers under fasting conditions with Ranitidine 300 mg tablets vs. the Canadian reference. The drug has shown that the products are bioequivalent (see table below).

Summary table of the comparative bioavailability data
Ranitidine (1 x 300 mg) tablets
From measured data (fasting state)

PARAMETER	Geometric Mean Arithmetic Mean (CV%)		% Ratio of Geometric Means
	Ranitidine Test	Zantac* Reference	
AUC_T (ng.h/mL)	6284.83 6420.4 (20.0)	5914.32 6093.7 (22.1)	106.3
AUC_I (ng.h/mL)	6426.05 6562.9 (20.0)	6064.72 6249.1 (22.2)	106.0
C_{max} (ng/mL)	1270.6000 1310.929 (24.2)	1186.7058 1249.501(28.5)	107.1
T_{max}^{*} (h)	2.900 (20.6)*	3.150 (28.7)*	
$T_{½}^{*}$ (h)	2.6096 (14.3)*	2.6868 (12.4)	

For T_{max}, $T_{½}$, the arithmetic mean only is presented.
* Zantac (Glaxo Welcome) purchased in Canada.

INDICATIONS

ratio-RANITIDINE tablets are indicated for the treatment of duodenal ulcer, benign gastric ulcer, reflux esophagitis, post-operative peptic ulcer, Zollinger-Ellison syndrome and other conditions where reduction of gastric secretion and acid output is desirable. These include treatment of NSAID-induced lesions (ulcers, erosions) and gastrointestinal symptoms and the prevention of their recurrence, prophylaxis of gastrointestinal hemorrhage from stress ulceration in seriously ill patients, the prophylaxis of recurrent hemorrhage from bleeding ulcers, and in the prevention of Acid Aspiration Syndrome (Mendelson's Syndrome) from general anesthesia in patients considered to be at risk for this, including obstetrical patients in labor, and obese patients.

In addition, ranitidine is indicated for the prophylaxis and maintenance treatment of duodenal or benign gastric ulcer in patients with a history of recurrent ulceration.

CONTRAINDICATIONS

ratio-RANITIDINE (ranitidine hydrochloride) is contraindicated for patients known to have hypersensitivity to ranitidine.

WARNINGS

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

Concomitant NSAID Use:
Regular supervision of patients who are taking NSAIDs concomitantly with ranitidine is recommended especially in the elderly and in those with a history of peptic ulcer. Baseline endoscopic and histological evaluation is necessary to rule out gastric carcinoma.

Patients with a History of Acute Porphyria:
Rare clinical reports suggest that ranitidine may precipitate acute porphyric attacks. Therefore, ranitidine should be avoided in patients with a history of acute porphyria.

Pregnancy:
The safety of ranitidine in the treatment of conditions where a controlled reduction of gastric secretion is required during pregnancy has not been established. Reproduction studies performed in rats and rabbits have revealed no evidence of ranitidine induced impaired fertility or harm to the fetus. Nevertheless, 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 fetus.

Lactation:
Ranitidine is secreted in breast milk in lactating mothers but the clinical significance of this has not been fully evaluated.

Children:
Experience with ranitidine in children is limited. It has however been used successfully in children aged 8 to 18 years in oral doses up to 150 mg twice daily.

PRECAUTIONS

Use in Impaired Renal Function:

Ranitidine is excreted via the kidneys and, in the presence of severe renal impairment, plasma levels of ranitidine are increased and elimination prolonged. Accordingly, it is recommended in such patients, to decrease the dosage of ranitidine by one-half. Accumulation with resulting elevated plasma concentrations will occur in patients with severe renal impairment (plasma creatinine concentration greater than 300 µmol/L); a recommended daily dose of oral ranitidine in such patients should be 150 mg. In patients undergoing chronic ambulatory peritoneal dialysis or chronic hemodialysis, a single oral dose of ranitidine 150 mg should be taken immediately after dialysis.

Drug Interactions:

Although ranitidine has been reported to bind weakly to cytochrome P_{450} in vitro, recommended doses of the drug do not inhibit the action of the hepatic cytochrome P_{450}-linked oxygenase enzymes. However, there have been isolated reports of drug interactions which suggest that ranitidine may affect the bioavailability of certain drugs (e.g. ketoconazole) by some mechanism as yet unidentified (e.g. a pH dependant effect on absorption or a change in volume of distribution).

As well, sporadic cases of drug interactions have been reported in elderly patients involving both hypoglycemic drugs and theophylline. The significance of these reports cannot be determined at present, as controlled clinical trials with theophylline and ranitidine have not shown interaction.

If high doses (2 g) of sucralfate are co-administered with ranitidine, the absorption of ranitidine may be reduced. This effect is not seen if sucralfate is taken at least 2 hours after ranitidine administration.

Geriatrics:

Since malignancy is more common in the elderly, particular consideration must be given to this before therapy with ranitidine is instituted. Elderly patients receiving NSAIDs concomitantly with ranitidine should be closely supervised.

As with all medication in the elderly, when prescribing ranitidine, consideration should be given to the patient's concurrent drug therapy. Sporadic cases of drug interaction have been reported in elderly patients involving both hypoglycemic drugs and theophylline. The significance of these reports cannot be determined at present, as controlled clinical trials with theophylline and ranitidine have shown no interaction. Elderly patients may be at increased risk for confusional states and depression.

ADVERSE EFFECTS

The following adverse reactions have been reported as events in clinical trials or in the routine management of patients treated with ranitidine. A cause and effect relationship to ranitidine is not always established.

CNS:
Headache, sometimes severe; malaise; dizziness; somnolence; insomnia; vertigo; and reversible blurred vision suggestive of a change in accommodation. Isolated cases of reversible mental confusion, agitation, depression, hallucinations have been reported, predominantly in severely ill elderly patients.

Cardiovascular:
Isolated reports of tachycardia, bradycardia, premature ventricular beats, AV block have been noted. Asystole has been reported in very few individuals with and without predisposing conditions following i.v. administration and has not been reported following oral administration of ratio-RANITIDINE (see Precautions and Dosage).

Gastrointestinal:
Constipation, diarrhea, nausea/vomiting and abdominal discomfort/pain.

Hepatic:
In normal volunteers, transient and reversible ALT (SGPT) and AST (SGOT) values were increased to at least twice the pretreatment levels in 6 of 12 subjects receiving ranitidine 100 mg q.i.d. i.v. for 7 days, and in 4 of 24 subjects receiving 50 mg q.i.d. i.v. for 5 days. Therefore, it may be prudent to monitor AST (SGOT) and ALT (SGPT) in patients receiving i.v. treatment for 5 days or longer and in those with pre-existing liver diseases. With oral administration, there have been occasional reports of hepatitis, hepatocellular or hepatocanalicular or mixed, with or without jaundice. In such circumstances, ranitidine should be discontinued immediately. These are usually reversible, but in exceedingly rare circumstances, death has occurred.

Musculoskeletal:
Rare reports of arthralgia and myalgia.

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

Endocrine:
No clinically significant interference with endocrine or gonadal function has been reported. There have been a few reports of breast symptoms in men taking ranitidine.

Dermatologic:
Rash, including cases suggestive of mild erythema multiforme.

Other:
Rare cases of hypersensitivity reactions (including chest pain, bronchospasm, fever, rash, eosinophilia, anaphylaxis, urticaria, angioneurotic edema, hypotension) and small increases in serum creatinine have occasionally occurred after a single dose. Acute pancreatitis has been reported rarely.

OVERDOSE SYMPTOMS AND TREATMENT

There is no experience to date with deliberate overdosage. The usual measures to remove unabsorbed drug from the gastrointestinal tract (including activated charcoal or syrup of ipecac), clinical monitoring and supportive therapy should be employed. Also, if need be, the drug can be removed from the plasma by hemodialysis.

DOSAGE

Duodenal ulcer and benign gastric ulcer:
300 mg once daily at bedtime or 150 mg twice daily taken in the morning and before retiring. It is not necessary to time the dose in relation to meals. In most cases of duodenal ulcer and benign gastric ulcer, healing will occur in 4 weeks. In the small number of patients whose ulcers may not have fully healed, these are likely to respond to a further 4 week course of treatment. In the treatment of duodenal ulcers, 300 mg twice daily for 4 weeks, may be of benefit when more rapid healing is desired.

Maintenance therapy:
Duodenal ulcers, benign gastric ulcers: Patients who have responded to short-term therapy, particularly those with a history of recurrent ulcer, may benefit from chronic maintenance therapy at a reduced oral tablet dosage of 150 mg once daily at bedtime.

In the management of duodenal ulcers, smoking is associated with a higher rate of ulcer relapse (up to 9.2 times higher in one trial), and such patients should be advised to stop smoking. In those patients who fail to comply with such advice, 300 mg nightly provides additional therapeutic benefit over the 150 mg once daily dosage regimen.

Reflux esophagitis:
Acute treatment: 300 mg once daily at bedtime, or alternatively 150 mg twice daily, taken in the morning and before retiring for up to 8 weeks. In patients with moderate to severe esophagitis, the dosage of ranitidine may be increased to 150 mg for 4 times daily up to 12 weeks. Long-term management: the recommended adult oral dose is 150 mg twice daily.

Post-operative peptic ulcer:
150 mg twice daily, taken in the morning and before retiring.

Pathological hypersecretory conditions (Zollinger-Ellison Syndrome):
150 mg three times daily may be administered initially. In some patients, it may be necessary to administer ratio-RANITIDINE 150 mg doses more frequently. Doses should be adjusted to individual patient needs. Doses up to 6 g/day have been well tolerated.

Treatment of NSAID-induced lesions (ulcers, erosions) and gastrointestinal symptoms and prevention of their recurrence: In ulcers following NSAID therapy or associated with continued NSAIDs, 150 mg twice daily for 8 to 12 weeks may be necessary. For the prevention of NSAID associated ulcer recurrence, 150 mg twice daily may be given concomitantly with nonsteroidal anti-inflammatory drug therapy.

Prophylaxis of Acid Aspiration Syndrome (AAS): 150 mg the evening prior to anesthesia induction is recommended, however, 150 mg 2 hours before anesthesia induction is also effective. In an emergency situation, the use of alkalis, antacids, and meticulous anesthetic technique is still necessary as ratio-RANITIDINE does not affect the pH and volume of the existing gastric content.

Prophylaxis of hemorrhage from stress ulceration in seriously ill patients or prophylaxis of recurrent hemorrhage in patients bleeding from peptic ulceration who are currently managed by i.v. ranitidine: an oral dose of 150 mg twice daily may be substituted for the injection once oral feeding commences.

Geriatrics:
For all conditions listed above, the drug dosage for the elderly who are seriously ill should start at the lowest recommended dose and be adjusted as necessary with close supervision.

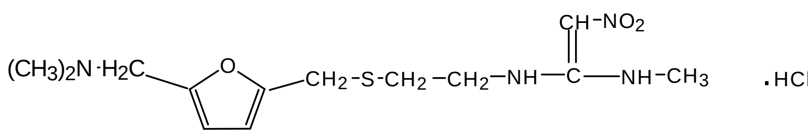
PHARMACEUTICAL INFORMATION

Drug Substance:

Proper name: ranitidine hydrochloride

Chemical name: (n-{2-[[(5-[(dimethylamino)-methyl]-2-furanyl]-methyl]thio]ethyl]-N'-methyl-2-nitroethene-1,1-diamine, hydrochloride.

Structural formula:



Empirical formula: $C_{13}H_{22}N_{4}0_{3}S \cdot HCl$

Molecular weight: 350.87 (as hydrochloride salt)

Description: Ranitidine hydrochloride is a white to pale yellow granular substance. At room temperature, ranitidine hydrochloride is soluble in water, methanol, ethanol and chloroform (decreasing order).

Composition: **Tablets: 150 mg:**
Each white to off-white, round, biconvex, film-coated tablets, embossed “rph” on one side and “R12" on the other side contains: ranitidine HCl 168 mg (equivalent to ranitidine anhydrous free base 150 mg). Non medicinal ingredients: magnesium stearate, microcrystalline cellulose, calcium hydrogen phosphate, maize starch, sodium starch glycollate and colloidal anhydrous silica. The film-coating suspension contains: lactose, methyl hydroxy-propylcellulose, titanium dioxide and macrogol 4000. Gluten- and tartrazine-free.

300 mg:
Each white to off-white, oblong, film-coated tablet, embossed “rph” on one side and "R11" on the other side contains: ranitidine HCl 335 mg (equivalent to ranitidine anhydrous free base 300 mg). Nonmedicinal ingredients: magnesium stearate, microcrystalline cellulose, calcium hydrogen phosphate, maize starch, sodium starch glycollate and colloidal anhydrous silica. The film-coating suspension contains: lactose, methylhydroxypropylcellulose titanium dioxide and macrogol 4000. Gluten- and tartrazine-free.

SUPPLIED

Tablets: 150 mg:
Each white to off-white, round, biconvex, film-coated tablet, embossed “rph” on one side and “R12" on the other side contains: Ranitidine HCl 168 mg (equivalent to ranitidine anhydrous free base 150 mg). Nonmedicinal ingredients: magnesium stearate, microcrystalline cellulose, calcium hydrogen phosphate, maize starch, sodium starch glycollate and colloidal anhydrous silica. The film-coating suspension contains: lactose, methylhydroxypropylcellulose, titanium dioxide and macrogol 4000. Gluten- and tartrazine-free. Packs of 60, and bottles of 60 and 500.
Store between 15° - 30°C.
Protect from light and moisture.

300 mg:
Each white to off-white, oblong, film-coated tablet, embossed “rph” on one side and "R 11" on the other side contains: ranitidine HCl 335 mg (equivalent to ranitidine anhydrous free base 300 mg). Nonmedicinal ingredients: magnesium stearate, microcrystalline cellulose, calcium hydrogen phosphate, maize starch, sodium starch glycollate and colloidal anhydrous silica. The film-coating suspension contains: lactose, methylhydroxypropylcellulose, titanium dioxide and macrogol 4000. Gluten- and tartrazine-free. Packs of 30.
Store between 15° - 30°C.
Protect from light and moisture.

STABILITY AND STORAGE RECOMMENDATIONS

Store between 15°C - 30°C. Protect from light and moisture.

PHARMACOLOGY

Animal Pharmacology

Ranitidine is a potent competitive reversible, selective antagonist of histamine at H_2-receptors *in vitro* and *in vivo*. Thus, ranitidine antagonized the actions of histamine at H_2-receptors in the rat isolated uterus and in the guinea pig isolated atrium. Ranitidine is not an anticholinergic agent. On a molar basis, ranitidine is 4 to 5 times more active than cimetidine with a pA_2 value of 7.2. In concentrations 1,000 times greater than those required to block H_2-receptors, it failed to block either H_1-receptors or muscarinic receptors in the guinea pig isolated ileum. The beta-adrenoceptor responses of that rat uterus and guinea pig atrium to isoprenaline were also unaffected by ranitidine.

Blockade of histamine H_2-receptors in the stomach *in vivo* is the pharmacological action of ranitidine with greatest immediate clinical relevance. Ranitidine inhibits gastric secretion induced by various secretagogues in both the rat and dog.

In the conscious dog with a Heidenhain pouch, raniditine given orally or intravenously antagonised gastric acid secretion induced by histamine, pentagastrin and bethanechol. Ranitidine was 5 to 10 times more active than cimetidine. However, both ranitidine and cimetidine had similar time curves of action. Ranitidine also inhibited the gastric secretory response to food in the conscious fistulated dog.

Ranitidine inhibited acid secretion in the perfused stomach of anaesthetised rat, and aspirin induced gastric lesion formation in the conscious rat, both in the presence and absence of excess hydrochloric acid. Measurements of the ratio of mucosal blood flow to acid secretion show that the inhibitory action of ranitidine upon gastric acid secretion cannot be attributed to changes in blood flow.

There were no behavioural effects in the mouse and rat after oral administration of 800 mg/kg ranitidine. Cats and dogs dosed with ranitidine 80 mg/kg orally, exhibited no behavioural effects indicative of an action on the central nervous system, although at this high dose level in the dog there was an indication of periperal vasodilation and skin irritation due to released histamine. Ranitidine, when coadministered with the following CNS modulating preparations; codeine, hexobarbitone, ethyl alcohol, chlordiazepoxide, chlorpromazine, imipramine, α-methyldopa, reserpine, apomorphine or pentylenetetrazol, did not alter the parmacological effects of either preparation.

At a dose level 45 times the anti-secretory ED_{50}, intravenous infusion of ranitidine had no effect on the heart rate, blood pressure or electrocardiogram of the anaesthetised dog. The respiratory system was unaffected by ranitidine after oral doses in the mouse, rat, rabbit, cat and dog and after intravenous doses in the dog.

In the conscious dog, ranitidine has no appreciable effect on blood pressure or heart rate when administered orally at 10 mg/kg. There were short-lived falls in diastolic blood pressure after an intravenous dose of 10 mg/kg, 370 times the antisecretory dose level. There was no evidence of arrhythmia nor of any electrocardiographic abnormality.

Long-term toxicity studies have shown that ranitidine does not possess antiandrogenic activity nor does it displace dihydrotestosterone from the androgen binding sites.

Metoclopramide, atropine, and aspirin in the rat produced no change in the anti-secretory activity of ranitidine.

The effect of ranitidine on anti-inflammatory drugs was varied. There was no effect on the anti-inflammatory action of prednisolone, but the anti-inflammatory action of indomethacin was enhanced. Administration of ranitidine reduced the frequency of aspirin and indomethacin induced gastric erosions. The antinociceptive action of aspirin was reduced after ranitidine treatment.

Ranitidine, unlike cimetidine, does not inhibit the hepatic mixed function oxygenase system. Spectal interaction studies have shown that whilst cimetidine binds strongly to cytochrome P_{450}, ranitidine has only weak affinity for this enzyme. Cimetidine is known to impair the metabolism of pentobarbitone and warfarin. In doses of up to 166 mg/kg in the rat, ranitidine had no effect on the pentobarbitone sleeping time or the parmacokinetics and pharmacodynamics of warfarin.

Metabolism, distribution and excretion

The metabolism of ranitidine hydrochloride has been studied in four species of laboratory animal (mouse, rat, rabbit and dog) using radio labelled drug. The drug was rapidly absorbed after oral administation. In the mouse, rat and rabbit between 30% and 60% of the administered radioactivity was excreted in the urine, the remainder being recovered in the faeces.

In the mouse, 47% was excreted in the urine within 24 hours. In the rat, N-demethylation of ranitidine was the major route of metabolism. 30% of the administered dose was excreted in the urine as unchanged drug, up to 14% as desmethylranitidine, 3-6% as the N-oxide and 4% as the S-oxide. In rat bile the major radioactive components were ranitidine and an unidentified metabolite known as “Fast-Running Metabolite” (FRM) which is thought to be a charge transfer complex of ranitidine with bile pigments.

In the rabbit, sulphoxidation of ranitidine was the major route of metabolism, 18% of the administered dose being excreted in the urine as unmetabolised ranitidine, 8% as S-oxide, 2-4% as the N-oxide, and 2-4% as desmethylranitidine.

In the dog up to 70% of the administered dose was excreted in the first 24 hours. About 40% of the drug was excreted in the urine as unchanged ranitidine and up to 30% as the N-oxide, N-oxidation being the main route of metabolism of ranitidine in the dog. The N-oxide was also the major radioactive component present in dog bile together with small amounts of unchanged ranitidine and FRM.

In the rat, rabbit and dog, less than 10.1% of ranitidine in plasma is protein bound. Within one to seven days of administration of radio-labelled drug in the rat and dog, over 99% of the radioactivity was cleared from the body. In common with many drugs, radioactivity persisted in the uveal tract of these two species, the half-life in the dog uveal tract being of the order of 6 months. Ranitidine and its S-oxide have greater affinity for melanin than the desmethyl metabolite; the N-oxide is bound only to a small extent.

The placental transfer of radioactive ranitidine and its metabolites has been studied in the pregnant rat and rabbit. Whole body autoradiography of rat and rabbit foetuses showed that small amounts of radioactivity were present in the uveal tract of the foetal eye in both species, in the gall bladder and intestine of the rabbit foetus and in the bladder of the rat foetus. Radioactivity was also detected in the salivary and mammary glands of the maternal rat and at very low concentration, in the milk.

Human pharmacokinetics

Serum concentrations necessary to inhibit 50% of stimulated gastric acid secretion are estimated to be 36 to 94ng/mL. Following a single oral dose of 150 mg, serum concentrations of ranitidine are in this range for up to 12 hours. There is a relationship between plasma concentratons of ranitidine and suppression of gastric acid production but wide interindividual variability exists.

Ranitidine is 50% absorbed after oral administration compared to an IV injection with mean peak levels of 440 to 545 ng/mL occurring two to three hours after a 150 mg does. The elimination half life is 1.5 to 3 hours.

Ranitidine is absorbed very rapidly after an intramuscular injection. Mean peak levels of 576 ng/mL occur within 15 minutes or less following a 50 mg intramuscular dose. Absorption from intramuscular sites is virtually complete, with a bioavailability of 90% to 100% compared with intravenous administration.

The principal route of excretion is the urine, with approximately 30% of the orally-administered dose collected in the urine as unchanged drug in 24 hours. Renal clearance is about 530 mL/min, indicating active tubular excretion, with a total clearance of 760 mL/min. The volume of distribution is 1.4 L/kg.

Studies in patients with hepatic dysfunction (compensated cirrhosis) indicate that there are minor, but clinically insignificant alterations in ranitidine half life, distribution, clearance and bioavailability.

Serum protein binding averages 15%.

The gastric antisecretory activity of ranitidine metabolites has been examined. In man, both the principal metabolite in the urine, the N-oxide (4% of the dose) and the S-oxide (1%) possess weak H_2-receptor blocking activity but desmethylraditidine (1%) is only 4 times less potent than ranitidine in the rat and half as potent as ranitidine in the dog.

Clinical Trials

In 6 clinical trials examining the healing of duodenal ulcers in 1500 patients, a dose of 300 mg daily for 4 weeks was found to have an 83% healing rate; however, increasing the dose to 300 mg twice daily gave significantly better results (92% healed at 4 weeks; $p<0.001$).

TOXICOLOGY

Toxicology, Impairment of Fertility, Carinogenesis, and Mutagenesis

Ranitidine hydrochloride has been subjected to exhaustive toxicological testing which has demonstrated the lack of any specific target organ or any special risk associated with its clinical use.

Acute Toxicity Studies

In mice and rats, the intravenous LD_{50} is of the order of 75 mg/kg, whereas orally, even doses of 1000 mg/kg are not lethal. In dogs, the oral minimum lethal dose is 450 mg/kg/day. High single doses of ranitidine (up to 80 mg/kg orally) show only minimal and reversible signs of toxicity, some of which are related to transitory histamine releases.

Long-term toxicity studies

In the long-term toxicity and carcinogenicity studies, very high doses of ranitidine were given daily to mice (up to 2000 mg/kg/day) throughout their normal life-span, and to dogs (up to 450 mg/kg/day) for periods of up to one year.

These doses produced massive plasma ranitidine concentrations far in excess of those found in human patients receiving ranitidine at the recommended therapeutic dose. For example, in the dogs, peak plasma concentrations were in excess of 115 μg/mL and in mice basal plasma levels were in the range of 4-9 μg/mL. In man, after oral administration of 150 mg ranitidine, the mean peak plasma concentration (C_{max}) was between 360 and 650 ng/mL.

In the rat, doses as high as 2000 mg/kg/day were well tolerated, the only morphological change seen was the increased of accumulations of foamy alveolar macrophages in the lungs. The accumulations of these cells is a natural phenomena in aging rats and chronic administration of a wide variety of drugs has been known to contribute to this process. Therefore, it is unlikely that the pharmacologic concentrations of ranitidine administered to these rats contributed to this natural process.

In the six-week and six-months oral studies in the dog (100 mg/kg/day) loose faeces were occasionally detected, while in the six-month study loose stools were accompanied on eight occasions by mucus-like material and sometimes by blood, mostly from one dog. Loose faeces, salivation and vomiting were observed in the 54-week dog study.

In isolated cases, dogs passed red-stained faeces which occasionally tested positive for occult blood. When the dose level was increased from 100 mg/kg/day to 225 - 450 mg/kg/day, no further red-stained faeces were seen, suggesting that any relationship to ranitidine is unlikely. Post-mortem examination of the dogs revealed no ranitidine-induced changes in the alimentary tract.
One dog had marginally raised levels of plasma alanine aminotransferase and alkaline phosphatase during the six-week study. This same dog also showed some necrotic foci in the liver. Small lesions of focal necrosis and fibrosis were also seen in one piece of liver from one female dog treated with 100 mg/kg for six months. No other differences were detected by light and electron microscopic examination of the treated and control livers. Since the focal lesions were seen in only one dog and were restricted to one piece of liver, it suggests

that they were not caused by ranitidine

Muscular tremors, an inability to stand, and rapid respiration were seen on occasion in dogs treated with 225 mg/kg/day in the 54-week study. The prevalence of these observations was increased when the dose was increased to a toxic level of 450 mg /kg /day. One dog died: no specific pathological changes or reason for the death was discovered.

Changes in the colour of granularity of the tapetum lucidum of the eye were detected in three dogs receiving the highest dose of ranitidine (450 mg/kg/day) during the 54-week study. In one dog, this change was considered to be related to treatment. The change, a pallor of the tapetum, was reversible. No changes were seen with light or electron microscopic examination of the eye. The changes in the tapetum are of no clinical significance in humans since (i) humans do not have a tapetum lucidum and (ii) the changes were only seen at toxic pharmacological concentrations of ranitidine.

The mean serum glutamic pyruvic transaminase values for dogs treated at 450 /mg/kg/day were significantly greater, albeit marginally, than the control values. These enzyme increases were not accompanied by any histological changes.

Studies in which ranitidine was administered parenterally were performed. No sign of specific local irritation attributable to ranitidine was detected. In the rat, no biochemical or histopathological changes were observed at intravenous dose levels as high as 20 mg/kg. Specifically, no significant changes were found in the veins or subcutis. Mild lesions in some muscle samples were observed: usually, the cells were basophilic and smaller than normal; and the nuclei were swollen, more numerous, and sometimes had migrated to the centre of the cell.

In the rabbit, slight infiltration of the pannicular muscle by mononuclear cells were noted. This minor subcutaneous reaction was uncommon and showed no group related distribution. There was no apparent difference in irritance between ranitidine injection and placebo injection. In the rat, intravenous ranitidine at dose levels of 5.0 and 10.0 mg/kg daily for 15 days and 28 days produced no treatment related changes of biological importance in the haematopoietic system.

In Beagle dogs, intravenous ranitidine injection in doses up to 10 mg/kg/day for 28 and 42 days, produced no drug-related change in circulating erythrocytes or leukocytes and had no adverse effects on the haematopoietic system. No dose related changes were seen in electrocardiograms of Beagle dogs receiving up to 10 mg/kg ranitidine by intravenous injection. At dosage levels of up to 30 mg/kg, administered twice daily to Beagle dogs for 14 or 15 days, intravenous ranitidine injection produced no changes of biological significance in haematology, clinical chemistry or urinalysis.

No changes were observed in the eyes of dogs (specifically the tapetum lucidum) receiving ranitidine in doses up to 30 mg/kg twice daily for 15 days. At intravenous doses above 1.25 mg/kg, ranitidine injection produced immediate and transient reactions in the Beagle dog. The following reactions were typically produced by the administration of 1.25 mg/kg: bloodshot eyes, closing and watering of eyes, defaecation, diarrhoea, erythema, flatus, licking of lips, running nose, salivation, subdued behaviour, swallowing, tachycardia, and trembling. The range and severity of the effects was aggravated by increased dosage.

Reproduction studies (Impairment of fertility)
Reproduction studies were carried out in the rat and rabbit.

Rats were exposed to ranitidine before and during mating, throughout pregnancy, lactation and during the weaning period. No effects on the reproductive process were seen and there was no evidence of an anti-androgenic effect.

A total of 2,297 foetuses from rats treated with ranitidine were examined. There was no evidence that ranitidine is a rat teratogen. Cleft palates occurred in foetuses from both treatment groups, however, there were significantly more in the control rat population.

A total of 944 foetuses from rabbits treated with ranitidine were examined; no drug related adverse events or abnormalities in the foetuses were observed.

Rabbits receiving a bolus intravenous injection of ranitidine (10 mg/kg) once daily on gestation days 7-16 exhibited a reduction in weight gain. Their foetuses weighed significantly less than foetuses of untreated controls. In addition, 12.4% of ranitidine-exposed foetuses had cleft palates. Reanalysis of this and a comparison study performed to assess reproducibility demonstrated a lack of data reproducibility. Therefore, the effects observed in the first trial are aberrant, and should not form the basis for maternal or foetal toxicity.

In the subsequent study, no evidence of maternal or foetal toxicity was observed in rabbits dosed with 100 mg/kg ranitidine orally during days 2-29 of pregnancy. The peak plasma levels of ranitidine after a 100 mg/kg oral dose are similar to those obtained one minute after a 10 mg/kg dose administered intravenously (20-25 μg/mL). Therefore, no teratogenic effects of ranitidine have been demonstrated at doses of 10 mg/kg (IV) and 100 mg/kg (Tablets) in rabbits.

Carcinogenicity studies
There is no evidence that ranitidine is a carcinogen. Long term toxicity and carcinogenicity studies have involved the treatment of 600 mice and 636 rats at doses up to 2,000 mg/kg for two years and 129 weeks respectively and 42 dogs at doses up to 450 mg/kg/day for periods up to one year. These dose levels are far in excess of those to be used therapeutically in man. None of these animals had any intestinal metaplasia. There was no evidence of a tumorigenic effect of ranitidine in any other tissue.

Mutagenesis
Ranitidine is not mutagenc at doses as great as 30 mg/plate in the Ames Assay utilizing *Salmonella typhimurium* (TA 1538, TA 98, TA 100 and TA 1537) or in doses of 9 mg/plate utilizing *Escherichia Coli* (WP2 and WP2 uvrA) with or without activation.

Ranitidine at concentrations of 20-30 mg/plate has a weak direct mutagenic actions in *S. typhimurium* TA 1535 and 9 mg/plate in *E coli* WP67. Ranitidine was not mutagenic at a concentration of 2 mg/mL in *E. coli* or *S. typhimurium* in the more sensitive oral solution microtitre fluctuation assay method. This weak direct matugenic effect is of no clinical significance; the magnitudes of ranitidine concentration used in these assays are thousands of times greater than that attained therapeutically in human plasma.

The principal metabolites of ranitidine in man were not significantly mutagenic. This conclusion is supported by the following experiment. A test solution obtained by interacting ranitidine. (10mM) and sodium nitrite (40mM) was mutagenic in *S. Typhimurium* (TA 1535) but not in *S. Typhimurium* (TA 1537) or *E. Coli* (WP67 or WP2 uvrA). This positive result is attributable to the presence of a nitrosonitrolic acid derivative AH 23729, which was mutagenic. When the sodium nitrite concentration was reduced to 15mM or less, the solution was not mutagenic in any of the test microorganisms. The formation of AH 23729 requires concentrations of nitrous acid far in excess of those encountered in any probable physiological conditions. The other nitrosation products were not mutagenic in any of the microorganisms tested. There is no reason, therefore, for supposing that ranitidine is likely to be mutagenic in animals or man as a consequence of nitrosation in the stomach.

There is no evidence from long term toxicology, carcinogenicity and mutagenicity studies in aninals to suggest that ranitidine is likely to have any deleterious effects in man when administered at therapeutic dose levels.

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