Ranitidine *(BAN, USAN, rINN)*

AH-19065; Ranitidiini; Ranitidin; Ranitidina; Ranitidinum. *NN*-Dimethyl-5-[2-(1-methylamino-2-nitrovinylamino)ethylthiomethyl]furfurylamine.

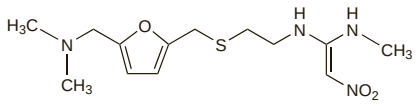
Ранитидин

$C_{13}H_{22}N_4O_3S$ = 314.4.

CAS — 66357-35-5.

ATC — A02BA02.

ATC Vet — QA02BA02.



Ranitidine Hydrochloride *(BANM, rINNM)*

AH-19065; Hidrocloruro de ranitidina; Ranitidiinihydrokloridi; Ranitidin Hidroklorür; Ranitidine, chlorhydrate de; Ranitidin-hidroklorid; Ranitidin-hydrochlorid; Ranitidinhydroklorid; Ranitidini hydrochloridum; Ranitidino hidrochloridas; Ranitydyny chlorowodorek.

Ранитидина Гидрохлорид

$C_{13}H_{22}N_4O_3S,HCl$ = 350.9.

CAS — 66357-59-3.

ATC — A02BA02.

ATC Vet — QA02BA02.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Jpn*, and *US*.

Ph. Eur. 6.2 (Ranitidine Hydrochloride). A white or pale yellow, crystalline powder. It exhibits polymorphism. Freely soluble in water; sparingly soluble or slightly soluble in dehydrated alcohol; very slightly soluble in dichloromethane. A 1% solution in water has a pH of 4.5 to 6.0. Store in airtight containers. Protect from light.

USP 31 (Ranitidine Hydrochloride). A white to pale yellow, practically odourless, crystalline powder. It is sensitive to light and to moisture. Very soluble in water; sparingly soluble in alcohol. A 1% solution in water has a pH of 4.5 to 6.0. Store in airtight containers. Protect from light.

Stability and incompatibility. References.

1. Chilvers MR, Lysne JM. Visual compatibility of ranitidine hydrochloride with commonly used critical-care medications. *Am J Hosp Pharm* 1989; **46:** 2057–8.
2. Wohlford JG, *et al.* More information on the visual compatibility of hetastarch with injectable critical-care drugs. *Am J Hosp Pharm* 1990; **47:** 297–8.
3. Williams MF, *et al.* In vitro evaluation of the stability of ranitidine hydrochloride in total parenteral nutrition mixtures. *Am J Hosp Pharm* 1990; **47:** 1574–9.
4. Galante LJ, *et al.* Stability of ranitidine hydrochloride at dilute concentration in intravenous infusion fluids at room temperature. *Am J Hosp Pharm* 1990; **47:** 1580–4.
5. Galante LJ, *et al.* Stability of ranitidine hydrochloride with eight medications in intravenous admixtures. *Am J Hosp Pharm* 1990; **47:** 1606–10.
6. Stewart JT, *et al.* Stability of ranitidine in intravenous admixtures stored frozen, refrigerated, and at room temperature. *Am J Hosp Pharm* 1990; **47:** 2043–6.
7. Montoro JB, Pou L. Comment on stability of ranitidine hydrochloride in total nutrient admixtures. *Am J Hosp Pharm* 1991; **48:** 2384.
8. Stewart JT, *et al.* Stability of ranitidine hydrochloride and seven medications. *Am J Hosp Pharm* 1994; **51:** 1802–7.
9. Crowther RS, *et al.* In vitro stability of ranitidine hydrochloride in enteral nutrient formulas. *Ann Pharmacother* 1995; **29:** 859–62.

Adverse Effects

As for Cimetidine, p.1716. Unlike cimetidine, ranitidine has little or no anti-androgenic effect, despite isolated reports of gynaecomastia and impotence.

◊ General references.

1. Wormsley KG. Safety profile of ranitidine: a review. *Drugs* 1993; **46:** 976–85.

Carcinogenicity. For a discussion of the possible association between histamine H_2-antagonists and cancer, including mention of a study with ranitidine, see Cimetidine, p.1717.

Effects on the blood. For a discussion of the adverse haematological effects of H_2-antagonists, see Cimetidine, p.1717.

Effects on the cardiovascular system. Similarly to cimetidine (p.1717), bradycardia,[1,2] AV block,[2] and cardiac arrest[3] have been reported rarely during ranitidine therapy. A positive inotropic effect, without significant changes in heart rate or blood pressure, has also been reported in healthy subjects[4] and pretreatment with ranitidine has blocked the cardiac depressant effects seen in some subjects given famotidine or nizatidine.[5] Although studies in critically ill patients[6] and healthy subjects[7,8] have found no adverse haemodynamic effects associated with ranitidine, it is likely that a small proportion of patients are more susceptible to the cardiovascular effects of ranitidine. Caution is recommended when ranitidine is given intravenously, particularly in patients with cardiovascular disease.

1. Johnson WS, Miller DR. Ranitidine and bradycardia. *Ann Intern Med* 1988; **108:** 493.
2. Tanner LA, Arrowsmith JB. Bradycardia and H antagonists. *Ann Intern Med* 1988; **109:** 434–5.
3. Hart AM. Cardiac arrest associated with ranitidine. *BMJ* 1989; **299:** 519.
4. Meyer EC, *et al.* Inotropic effects of ranitidine. *Eur J Clin Pharmacol* 1990; **39:** 301–3.
5. Mescheder A, *et al.* Changes in the effects of nizatidine and famotidine on cardiac performance after pretreatment with ranitidine. *Eur J Clin Pharmacol* 1993; **45:** 151–6.
6. Vohra SB, *et al.* The haemodynamic effects of ranitidine injected centrally in optimally resuscitated patients. *Br J Hosp Med* 1989; **42:** 149.
7. Hughes DG, *et al.* Cardiovascular effects of H -receptor antagonists. *J Clin Pharmacol* 1989; **29:** 472–7.
8. Hilleman DE, *et al.* Impact of chronic oral H -antagonist therapy on left ventricular systolic function and exercise capacity. *J Clin Pharmacol* 1992; **32:** 1033–7.

Effects on the endocrine system. Unlike cimetidine (p.1717), ranitidine does not bind to androgen receptors and has little, if any, anti-androgenic effect. Studies in men taking ranitidine for the management of duodenal ulcer[1,2] reported no significant changes in the plasma concentrations of testosterone, luteinising hormone, follicle-stimulating hormone, or prolactin after up to 2 years of treatment; no significant changes in sperm concentration, motility, or morphology were noted.[1] There have been isolated reports of gynaecomastia,[3] loss of libido,[4] and impotence[5] associated with ranitidine, but in 9 patients with cimetidine-induced breast changes and impotence, transfer to ranitidine resulted in resolution of these symptoms.[6]

1. Wang C, *et al.* Ranitidine does not affect gonadal function in man. *Br J Clin Pharmacol* 1983; **16:** 430–2.
2. Knigge U, *et al.* Plasma concentrations of pituitary and peripheral hormones during ranitidine treatment for two years in men with duodenal ulcer. *Eur J Clin Pharmacol* 1989; **37:** 305–7.
3. Tosi S, Cagnoli M. Painful gynaecomastia with ranitidine. *Lancet* 1982; **i:** 160.
4. Smith RN, Elsdon-Dew RW. Alleged impotence with ranitidine. *Lancet* 1983; **ii:** 798.
5. Kassianos GC. Impotence and nizatidine. *Lancet* 1989; **i:** 963.
6. Jensen RT, *et al.* Cimetidine-induced impotence and breast changes in patients with gastric hypersecretory states. *N Engl J Med* 1983; **308:** 883–7.

Effects on the eyes. For a report of an increase in intra-ocular pressure associated with ranitidine, see under Cimetidine, p.1717. A cohort study involving 140 128 patients receiving anti-ulcer therapy, 70 389 of whom received ranitidine, found no evidence that any of the drugs studied were associated with a major increased risk of vascular or inflammatory disorders of the eye.[1]

For reference to loss of colour vision in a child receiving ranitidine see under Effects on the Nervous System, below.

1. García Rodríguez LA, *et al.* A cohort study of the ocular safety of anti-ulcer drugs. *Br J Clin Pharmacol* 1996; **42:** 213–16.

Effects on the kidneys. For reference to interstitial nephritis associated with H_2-antagonists including ranitidine, see under Cimetidine, p.1717.

Effects on the liver. There have been some case reports of ranitidine hepatotoxicity.[1-3] The increase in relative risk seen in a large cohort study involving 108 891 patients receiving antisecretory therapy was less for ranitidine (1.7:1) than for cimetidine (see p.1717).

1. Souza Lima MA. Ranitidine and hepatic injury. *Ann Intern Med* 1986; **105:** 140.
2. Ramrakhiani S, *et al.* Possible cholestatic injury from ranitidine with a review of the literature. *Am J Gastroenterol* 1998; **93:** 822–6.
3. Liberopoulos EN, *et al.* Possible ranitidine-induced cholestatic jaundice. *Ann Pharmacother* 2002; **36:** 172.

Effects on the nervous system. Ranitidine has been associated with adverse neurological effects including confusion,[1-8] loss of colour vision,[4] aggressiveness,[2,4,6] lethargy,[8] somnolence,[8] disorientation,[8] depression,[8] hallucinations,[1,7-9] and severe headache.[10] As with cimetidine (p.1717) these reactions occur mainly in the elderly, the severely ill, or patients with renal or hepatic impairment. Single-dose studies in young healthy subjects have found no adverse changes in performance, CNS function, or subjective assessment of mood after oral doses of ranitidine 150 or 300 mg.[11]

1. Hughes JD, *et al.* Mental confusion associated with ranitidine. *Med J Aust* 1983; **2:** 12–13.
2. Silverstone PH. Ranitidine and confusion. *Lancet* 1984; **i:** 1071.
3. Epstein CM. Ranitidine and confusion. *Lancet* 1984; **i:** 1071.
4. De Giacomo C, *et al.* Ranitidine and loss of colour vision in a child. *Lancet* 1984; **ii:** 47.
5. Mani RB, *et al.* H -receptor blockers and mental confusion. *Lancet* 1984; **ii:** 98.
6. Mandal SK. Psychiatric side effects of ranitidine. *Br J Clin Pract* 1986; **40:** 260.
7. MacDermott AJ, *et al.* Acute confusional episodes during treatment with ranitidine. *BMJ* 1987; **294:** 1616.
8. Slugg PH, *et al.* Ranitidine pharmacokinetics and adverse central nervous system reactions. *Arch Intern Med* 1992; **152:** 2325–9.
9. Price W, *et al.* Ranitidine-associated hallucinations. *Eur J Clin Pharmacol* 1985; **29:** 375–6.
10. Epstein CM. Ranitidine. *N Engl J Med* 1984; **310:** 1602.
11. Nicholson AN, Stone BM. The H -antagonists, cimetidine and ranitidine: studies on performance. *Eur J Clin Pharmacol* 1984; **26:** 579–82.

Effects on the skin. A report of vasculitic rash occurring in 3 patients undergoing ranitidine therapy.[1] In each case the rash cleared after withdrawal of the drug.

See also under Hypersensitivity, below, and also Cimetidine, p.1717.

1. Haboubi N, Asquith P. Rash mediated by immune complexes associated with ranitidine treatment. *BMJ* 1988; **296:** 897.

Fever. A report[1] of pyrexia associated with ranitidine. Apart from raised temperature the patient was otherwise well; fever resolved on stopping ranitidine and recurred on rechallenge.

1. Kavanagh GM, *et al.* Ranitidine fever. *Lancet* 1993; **341:** 1422.

Hypersensitivity. Respiratory stridor and an urticarial rash occurred in a patient shortly after taking the first dose of ranitidine;[1] the symptoms responded to adrenaline subcutaneously.

1. Brayko CM. Ranitidine. *N Engl J Med* 1984; **310:** 1601–2.

Meningitis. A 30-year-old man developed aseptic meningitis on 3 occasions after use of ranitidine.[1] In each case symptoms resolved rapidly on withdrawal of the drug.

1. Durand JM, *et al.* Ranitidine and aseptic meningitis. *BMJ* 1996; **312:** 886. Correction. *ibid.*; 1392.

Precautions

As for Cimetidine, p.1718.

Helicobacter pylori testing. For reference to the effect of ranitidine on the urea breath test for *Helicobacter pylori*, see p.1718.

Hepatic impairment. Sixteen of 27 patients with cirrhosis of the liver and indications for treatment with an H_2-antagonist (peptic ulcer, gastritis, or reflux oesophagitis) failed to respond to ranitidine 300 mg compared with 6 failures from 32 patients without cirrhosis. Famotidine 40 mg was given to 10 of the cirrhotic nonresponders and 8 still had no response; 7 of these patients were given cimetidine 800 mg and only 1 responded. In the control group, all 3 patients given famotidine did not respond and only 1 responded when given cimetidine. It was concluded that the incidence of non-response to H_2-antagonists is increased in patients with liver cirrhosis but no explanation could be given for this effect.[1] Interestingly there is an earlier report of patients with cirrhosis demonstrating increased bioavailability and decreased clearance of ranitidine.[2]

1. Walker S, *et al.* Frequent non-response to histamine H -receptor antagonists in cirrhotics. *Gut* 1989; **30:** 1105–9.
2. Young CJ, *et al.* Effects of cirrhosis and ageing on the elimination and bioavailability of ranitidine. *Gut* 1982; **23:** 819–23.

Porphyria. Ranitidine is considered to be unsafe in patients with porphyria although there is conflicting experimental evidence of porphyrinogenicity.

Renal impairment. For evidence of reduced clearance of ranitidine in patients with renal impairment see Administration in Renal Impairment, below.

Interactions

Unlike cimetidine (p.1718), ranitidine does not seem to affect cytochrome P450 to any great extent, and therefore is considered to have little effect on the metabolism of other drugs. However, as with other H_2-antagonists, its effects on gastric pH may alter the absorption of some other drugs.

◊ A review comparing the drug interactions of ranitidine with those of cimetidine.[1]

1. Smith SR, Kendall MJ. Ranitidine versus cimetidine: a comparison of their potential to cause clinically important drug interactions. *Clin Pharmacokinet* 1988; **15:** 44–56.

Cisapride. Peak plasma concentrations of ranitidine were achieved more rapidly in 12 healthy subjects who also took cisapride.[1] The clinical significance is questionable and such combinations have been used clinically, although the use of cisapride is now restricted in most countries.

1. Rowbotham DJ, *et al.* Effect of single doses of cisapride and ranitidine administered simultaneously on plasma concentrations of cisapride and ranitidine. *Br J Anaesth* 1991; **67:** 302–305.

Pharmacokinetics

Ranitidine is readily absorbed from the gastrointestinal tract with peak concentrations in plasma occurring about 2 to 3 hours after oral doses. Food does not significantly impair absorption. The bioavailability of ranitidine after oral doses is about 50%. Ranitidine is rapidly absorbed on intramuscular injection, with peak plasma concentrations occurring in about 15 minutes. It is weakly bound, about 15%, to plasma proteins.

The elimination half-life is about 2 to 3 hours and is increased in renal impairment. A small proportion of ranitidine is metabolised in the liver to the *N*-oxide, the *S*-oxide, and desmethylranitidine; the *N*-oxide is the major metabolite but accounts for only about 4 to 6% of a dose. About 30% of an oral dose and 70% of an intravenous dose is excreted unchanged in the urine in