Ranitidine

Newborn Use Only

2017

Alert	Exposure to H_2 receptor antagonists may be associated with increased risk of NEC, infections and mortality in preterm infants and its use needs to balance safety against risks.
Indication	Treatment of gastroesophageal reflux disease (GORD) Post-operative prophylaxis in congenital tracheoesophageal fistula and oesophageal atresia Prophylaxis to reduce stress gastric ulcers/gastrointestinal haemorrhage Treatment of bradycardias attributed to GOR (not recommended)
Action	Ranitidine is a histamine$_2$ receptor antagonist. Ranitidine decreases acid secretion by inhibiting histamine$_2$ receptors on gastric parietal cells.
Drug Type	Histamine$_2$ receptor antagonist
Trade Name	APO-Ranitidine Tablets [Apotex]; Ausran Tablets [Aspen]; Chemists' Own Ranitidine Forte Tablets [Chemists' Own]; GenRx Ranitidine Tablets [Apotex]; Ranitidine Sandoz Tablets [Sandoz], Zantac Dispersible tablets [Aspen]; Zantac Effervescent tablets [Aspen]; Zantac Syrup [Aspen]; Zantac Tablets [Aspen] Ranitidine Sandoz Injection 50 mg/5 mL [Sandoz]; Zantac Concentrate for injection [Aspen]
Presentation	150 mg tablet 150 mg/10 mL liquid (contains ~7.5% w/v ethanol), 300 mL Zantac: 25 mg/mL, 2 mL injection (50 mg in 2 mL) Ranitidine Sandoz: 10 mg/mL, 5 mL injection (50 mg in 5 mL)
Dosage / Interval	Oral: 2 mg/kg/dose every 8 hours[21] IV Dose:[20] Term neonate — 1.5 mg/kg/dose every 8 hours Preterm (< 37 weeks) neonate — 0.5 mg/kg/dose every 12 hours Continuous IV infusion: 30–60 micrograms/kg/hour[22]
Maximum daily dose	
Route	PO, IV
Preparation/Dilution	**Oral** Administer undiluted. **IV bolus** CAUTION: There are two vial concentrations available. If using the 50 mg/2 mL injection draw up 1 mL (25 mg of ranitidine) and add 9mL of sodium chloride 0.9%, glucose 5% or glucose 10% to make a final volume of 10mL with a concentration of 2.5 mg/mL solution. If using 50 mg/5 mL injection, draw up 2.5 mL (25 mg of ranitidine) and add 7.5mL of sodium chloride 0.9%, glucose 5% or glucose 10% to make a final volume of 10mL with a concentration of 2.5 mg/mL solution. **Continuous infusion** Use the 50 mg/2 mL injection (Zantac) for IV infusion: Draw up 0.2 mL/kg (5 mg/kg of ranitidine) and make up to 50 mL with sodium chloride 0.9%, glucose 5% or glucose 10%. Infuse at a rate of 1 mL/hour = 100 microg/kg/hour Ranitidine Sandoz 50 mg/5 mL injection has no stability data at room temperature and therefore not recommended for IV infusion.
Administration	IV bolus: Administer dose over at least 5 minutes.
Monitoring	Nil
Contraindications	Patients with known hypersensitivity to any component of the preparation.
Precautions	Caution should be observed in patients with hepatic dysfunction since ranitidine is metabolised by the liver. Ranitidine is excreted via the kidneys. In the presence of severe

	renal impairment, plasma concentrations of ranitidine are increased and elimination prolonged. Bradycardia — ensure recommended rates of administration as not exceeded.
Drug Interactions	Amiodarone — concurrent use of amiodarone and ranitidine may result in increased amiodarone exposure.
Adverse Reactions	Exposure to H_2 receptor antagonists may be associated with increased risk of NEC in preterm infants.[8,10,18] The use of ranitidine in infants admitted to the NICU increases the risk of late-onset sepsis.[9,13,19] Use of H_2 blockers was an independent risk factor for *Candida parapsilosis*.[14] Exposure to gastric acid-suppression therapy is associated with health care- and community-associated *Clostridium difficile* infection in children.[5,6] Transient and reversible changes in liver function tests may occur. In some infants, H_2RA therapy causes irritability, head banging, headache, somnolence and other side effects which, if interpreted as persistent symptoms of GERD, could result in an inappropriate increase in dosage. Therapy with gastric acidity inhibitors increases the risk of acute gastroenteritis and community-acquired pneumonia in children.[13]
Compatibility	Fluids: Glucose 5%, glucose 10%, Hartmann's, sodium bicarbonate 4.2%, sodium chloride 0.9% Y-site: Aciclovir, adrenaline (epinephrine) hydrochloride, amifostine, aminophylline, anidulafungin, atracurium, aztreonam, bivalirudin, cefoxitin, ceftaroline fosamil, ciprofloxacin, cisatracurium, dexmedetomidine, dobutamine, dopamine, doripenem, esmolol, ethanol, filgrastim, fluconazole, foscarnet[3], glyceryl trinitrate, granisetron, heparin sodium, labetalol, linezolid, lorazepam, midazolam, milrinone, pancuronium, piperacillin-tazobactam (EDTA-free), remifentanil, tigecycline, vecuronium, zidovudine
Incompatibility	Fluids: TPN Y-site: Caspofungin, levomepromazine, phenobarbitone, sugammadex
Stability	Diluted IV solution using 50 mg/2 mL injection: Stable for 24 hours
Storage	Ampoule: Store below 25°C and protect from light. Tablets: Store below 30°C. Liquid: Store below 25°C.
Special Comments	
Evidence summary	**<u>Treatment of gastroesophageal reflux disease (GORD)</u>** <u>NICE Guidelines[1]</u> 1. Do not offer acid-suppressing drugs, such as proton pump inhibitors (PPIs) or H_2 receptor antagonists (H_2RAs), to treat overt regurgitation in infants and children occurring as an isolated symptom. 2. Consider a 4-week trial of a PPI or H_2RA for those who are unable to tell you about their symptoms (for example, infants and young children, and those with a neurodisability associated with expressive communication difficulties) who have overt regurgitation with 1 or more of the following: Unexplained feeding difficulties (for example refusing feeds, gagging or choking), distressed behaviour, faltering growth. 3. Consider a 4-week trial of a PPI or H_2RA for children and young people with persistent heartburn, retrosternal or epigastric pain. 4. Assess the response to the 4-week trial of the PPI or H_2RA, and consider referral to a specialist for possible endoscopy if the symptoms do not resolve or recur after stopping the treatment. 5. When choosing between PPIs and H_2RAs, take into account: the availability of age-appropriate preparations, the preference of the parent (or carer), child or young person (as appropriate) and local procurement costs. 6. Offer PPI or H_2RA treatment to infants, children and young people with endoscopy-proven reflux oesophagitis and consider repeat endoscopic examinations as necessary to guide subsequent treatment.

7. Do not offer metoclopramide, domperidone or erythromycin to treat GOR or GORD without seeking specialist advice and taking into account their potential to cause adverse events.

ESPGHAN and NASPGHAN Guidelines[2]

For healing of erosive esophagitis and relief of GERD symptoms, PPIs are superior to H_2RAs. Both medications are superior to placebo. Administration of long-term acid suppression without a diagnosis is inadvisable. When acid suppression is required, the smallest effective dose should be used. Most patients require only once-daily PPI; routine use of twice-daily dose is not indicated. No PPI has been approved for use in infants < 1 year of age and there are special concerns pertaining to prescription of PPIs in infants, as described in the Guideline.

H_2RAs exhibit tachyphylaxis or tolerance but PPIs do not. Tachyphylaxis is a drawback to chronic use. H_2RAs have a rapid onset of action and, like buffering agents, are useful for on-demand treatment.

Post-operative prophylaxis in congenital oesophageal atresia and tracheoesophageal fistula

In a systematic review by Shawyer et al,[3] of 25 articles (1,663 patients for analysis), most were single center studies (92 %) and retrospective (76 %); there were no randomised controlld trials. The quality of literature regarding anti-reflux medication for GER post EA-TEF repair is poor.

Treatment of bradycardias attributed to GOR in preterm infants

Wheatley et al,[12] in a randomised, controlled, masked cross-over study, compared metoclopramide, 0.2 mg/kg/dose q 6 hours, and ranitidine, 2 mg/kg/dose q 8 hours, with saline placebo. Each infant served as his own control. Preterm infants having > 3 bradycardic episodes per 2 days were eligible if the clinician intended to begin anti-reflux medications for bradycardia attributed to GER. Anti-reflux medications did not reduce, and may have increased, bradycardia episodes in preterm infants with GER. Ranitidine is not recommended for this indication.

Prophylactic therapy to reduce stress ulcers/GI haemorrhage

In a RCT by Kuusela et al,[15] ranitidine was given prophylactically after birth for 4 days to 48 infants mechanically ventilated and treated in the neonatal ICU. The gastric mucosa was both visually and histologically evaluated after 3 to 6 days. In the 23 infants prophylactically treated with ranitidine, the gastric mucosa was visually classified as normal in 14 (61%) infants as compared with five (20%) of 25 controls ($p < 0.004$). Histological lesions showed parallel results(57% vs. 16%, $p < 0.004$). Eight gastric ulcers were diagnosed endoscopically in the control group vs. none in the treatment group. The ulcers were all clinically 'silent' at the time of endoscopy. According to logistic regression modelling, the relative risk for gastric mucosal lesions in infants receiving prophylactic ranitidine was 0.03 (95% confidence interval 0.003 to 0.178).

Pourarian et al,[16] in another RCT, evaluated the effects of short-term prophylactic ranitidine in controlling gastric pH and prevention of GI bleeding in 80 neonates. They were randomly divided into case and control groups and their gastric pH, stool occult blood and macroscopic bleeding were determined. Intravenous ranitidine was administrated (5 mg/kg/day) for four days in the case group. Their gastric pH was measured before, one hour and two or three days after injection and prophylactic treatment was considered successful if gastric pH was > 4. Upper GI bleeding was observed in 41% of all patients. After ranitidine, there was a significant increase in gastric pH which was accompanied by a reduction in the frequency of upper GI bleeding. Furthermore, no significant changes were noted in the gastric pH of control group.

	Pharmacokinetics Preterm infants need significantly smaller doses of intravenous ranitidine than term neonates to keep their intraluminal gastric pH over 4. The required optimal dose of intravenous ranitidine for preterm infants is 0.5 mg/kg/body weight twice a day and that for term infants 1.5 mg/kg body weight three times a day.[20] Ranitidine (2 mg/kg per dose orally) reduced the time that gastric pH was < 4.0 by 44% when given twice daily and by 90% when given 3 times per day.[21] Target serum ranitidine concentrations effective in reducing gastric acid output probably vary with the gestational and postnatal age of the patient and with the underlying medical disorder (for example, acute stress). Concentrations between 40 and 60 ng/mL were found to suppress unstimulated gastric secretion by 90% in children aged up to 16 years with peptic ulcer disease; Eddlestone et al found the gastric pH to be maintained above 3–5 by serum concentrations greater than 200 ng/mL. Concentrations greater than 100 and 200 ng/mL could be expected for at least 12 hours after a single intravenous bolus of 1.6 and 3.3 mg/kg respectively; the same average concentration range could be obtained at steady state by continuous intravenous infusion at a rate between 0 03–0.06 mg/kg/hour.[22] **Safety** More et al,[18] performed a systematic review on the safety of H_2-blockers in preterm infants. One case-control and one prospective cohort study (n = 11,346), both evaluating H_2-blockers as IGA (inhibitors of gastric acid), were included. Meta-analysis showed a significant association between NEC and IGA (odds ratio [OR]: 1.78, 95% confidence interval [CI]: 1.4; 2.27, p < 0.00001). The prospective cohort study found a higher incidence of infection (sepsis, pneumonia, urinary tract infection) with IGA (37.4% versus 9.8%, OR: 5.5, 95% CI: 2.9 to 10.4, p < 0.001). Meta-analysis concluded that exposure to H_2 receptor antagonists may be associated with increased risk of NEC and infections in preterm infants.(LOE ?1 or II, GOR B) Terrin G, et al,[9] in a multicentre, prospective observational study involving 274 VLBW newborns with birth weight between 401 and 1500 g or gestational age between 24 and 32 weeks showed that risk of NEC was 6.6-fold higher in ranitidine-treated VLBW infants than in control subjects. Mortality rate was also significantly higher in newborns receiving ranitidine (9.9% vs 1.6%, P = 0.003). (LOE II, GOR B) There were other retrospective case series reporting similar increases in NEC.[8,10] Saiman et al, in a multicentre, prospective observational study involving 2157 infants in 6 NICUs in Canada showed that H_2 blockers was an independent risk factor for *C. parapsilosis*.[14] (LOEII, GOR C)
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