The effect of intravenous ranitidine on the intragastric pH of preterm infants receiving dexamethasone

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Abstract

Gastric perforation is a catastrophic, albeit uncommon, side effect of steroid treatment for premature infants with bronchopulmonary dysplasia (BPD). A reduction of intragastric acidity may protect against peptic ulceration. The effect of different doses of ranitidine, given as intravenous infusions, on intragastric acidity in premature neonates was therefore examined. Ten consecutive, enterally starved, infants receiving dexamethasone (0.6 mg/kg) for BPD were enrolled. Intragastric pH was continuously monitored on the day before steroid treatment and on the four following days, initially without H₂ blockade and then using a continuous intravenous infusion of ranitidine at 0.031, 0.0625, and 0.125 mg/kg/hour. An infusion of 0.0625 mg/kg/hour of ranitidine was sufficient to increase and maintain gastric pH above 4; the authors therefore use this infusion during dexamethasone administration as possible prevention of gastric perforation. (*Arch Dis Child* 1993; 69: 37-39)

Bronchopulmonary dysplasia (BPD) remains a major cause of mortality and morbidity among the survivors of neonatal intensive care. Dexamethasone has been shown to be an effective treatment for BPD,¹ but it is an agent with many potential adverse effects. One important and potentially life threatening side effect previously reported from this unit² and elsewhere³ is gastrointestinal bleeding and perforation. This has a reported incidence of about 2%.¹ In addition, gastro-oesophageal reflux occurs more commonly in very low birthweight babies⁴ and in babies with BPD treated with steroids.⁵ This may cause both oesophagitis and pulmonary aspiration of gastric contents.⁶

Principal among factors predisposing to these problems is the presence of acid in the stomach. This has been the subject of much debate, but it is now widely accepted that within 24 hours of birth the preterm infant is capable of producing a gastric pH of less than 2.⁷ Although other factors, notably steroid inhibition of prostaglandin synthesis, may play a part in the aetiology of peptic ulceration, reduction of intragastric acidity remains the main therapeutic approach to prevention.

The effectiveness of histamine H₂ receptor blockade in raising gastric pH has been shown in infants and older children.⁸ Cimetidine and ranitidine have both been used successfully in infants with reflux oesophagitis,⁹ steroid

induced gastrointestinal bleeding,⁹ and acute gastric haemorrhage.¹⁰ However, few data exist regarding the efficacy of these agents in premature babies. In 1985 Hyman *et al* raised a question regarding the use of histamine antagonists in infants of below 32 weeks' gestation by demonstrating that Histalog (a histamine agonist and potent secretagogue) did not lead to an increase in gastric acid secretion, and concluded that the histamine receptor is non-functional at this time or else acid secretion is already maximal without histaminergic drive.¹¹

To determine whether H₂ receptor antagonists are effective in increasing gastric pH in preterm babies receiving steroids for BPD we have continuously recorded gastric pH in 10 infants receiving dexamethasone and various concentrations of ranitidine.

Patients and methods

Ten premature babies with BPD receiving a course of dexamethasone (0.6 mg/kg/day) on the neonatal intensive care unit at St James's University Hospital, Leeds were enrolled in this study over a six month period. The babies were at least 2 weeks old and dependent on intermittent positive pressure ventilation or supplementary oxygen treatment. All the babies received parenteral nutrition throughout the period of the study, as it is the policy of the unit to delay oral feeds until the infant is able to breathe independently of the ventilator, and no oral drugs were given until after the study had been completed. None of the babies studied had any known gastrointestinal disturbance.

Ethical approval for this study was obtained from the local research (ethics) committee and informed parental consent was obtained.

A monocrystalline antimony electrode (Synectics) was used to record gastric pH. The probe was calibrated using two non-phosphate buffer solutions (pH 7 and pH 2), before insertion and daily during use. Probe position in the body of the stomach was confirmed on day 1 using radiography. On the subsequent days the probe was passed the same distance as on day 1. Gastric pH was continuously monitored for 24 hours for each of 5 days using a Medilog 1010 recording box (Oakfield Instruments).

The treatment schedule was as follows: day 1, pretreatment day (baseline measurements); day 2, dexamethasone and no ranitidine; day 3, dexamethasone and 0.031 mg/kg/hour of ranitidine; day 4, dexamethasone and

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The median gastric pH of all the infants studied on each day (see text for treatment schedule)

Infant No	Day 1	Day 2	Day 3*	Day 4*†	Day 5*†
1	1.7	1.7	2.2	4.3	4.4
2	1.9	2.0	2.7	4.7	5.1
3	1.7	1.6	2.7	4.3	4.9
4	1.7	1.8	2.5	4.9	5.1
5	2.1	1.8	3.2	4.8	4.7
6	2.0	1.9	3.1	5.1	4.5
7	1.3	1.5	2.9	4.6	4.8
8	2.3	2.1	2.5	4.2	5.1
9	1.7	1.6	2.4	4.2	4.8
10	1.5	1.9	2.6	4.6	4.6

* $p < 0.001$ comparing with pretreatment days; † $p < 0.001$ comparing with low dose ranitidine day.

0.0625 mg/kg/hour of ranitidine; and day 5, dexamethasone and 0.125 mg/kg/hour of ranitidine. The ranitidine was given in 5% dextrose as a continuous intravenous infusion, this is the method of administration recommended by the manufacturers for neonates to avoid possible cardiac dysrhythmias.

The intragastric pH data from each subject was analysed using FLGAST (Oakfield Instruments) on a desk top computer to produce half hourly median pH values for each subject throughout the 24 hours. However, as pH is a logarithmic scale these data cannot be used to assess acid inhibition. The pH values were therefore converted to their equivalent hydrogen ion activity and, for each patient, the area under curve of hydrogen ion activity against time for each day was calculated. This is expressed as the 24 hour integrated gastric acidity.

To avoid any possible effect of an accumulation of dose, the data were recorded when a 'steady state' of acid inhibition had been achieved within 30 minutes of the start of each treatment period.

Statistical analysis of the data was performed using the Mann-Whitney test for non-parametric data.

Results

Gastric pH was continually monitored for five days in all 10 infants studied. The 10 infants were all very low birthweight infants with BPD requiring prolonged oxygen treatment. The

The median 24 hour integrated gastric acidity and range for the 10 infants receiving ranitidine.

median (range) gestation was 27.5 (24–31) weeks, birth weight 921 (579–1300) g, and postnatal age 17.5 (15–21) days. The median postnatal age at the start of steroid treatment was 18.5 days (range 16–22).

After treatment with dexamethasone nine out of the 10 infants showed a decrease in supplementary oxygen requirements (one infant remained ventilator dependent for several months and died). None of the infants showed any evidence of gastric bleeding or peptic ulceration.

A number of side effects of ranitidine treatment have been documented including changes in liver function tests, leucopenia, thrombocytopenia, agranulocytosis, and bradycardia. These side effects are all transient and reversible and during the study none of the infants suffered from any of these side effects.

Gastric pH was displayed and the median gastric pH (table) and 24 hour integrated gastric acidity were determined for each infant on each of the five days. Median 24 hour integrated gastric acidity initially showed a wide variation between babies but did not change when steroids were given on day 2 (figure).

The median and range gastric pH was not different on the pretreatment day (1.7, 1.3–2.3) and during the first day of steroids without ranitidine (1.8, 1.5–2.1). Gastric pH was, however, significantly higher and integrated gastric acidity significantly lower ($p < 0.001$), when the infants were receiving ranitidine treatment regardless of dose. There was no difference in pH between an infusion of 0.0625 and 0.125 mg/kg/hour at both doses gastric pH was raised and maintained at above 4, median (range) pHs of 4.6 and 4.8 (4.2–5.1 and 4.4–5.1). Infusion at the lower rate (0.031 mg/kg/hour), however produced a lesser elevation of median pH to 2.65 (2.2–3.2), ($p < 0.001$).

Discussion

Dexamethasone has revolutionised the treatment of infants with chronic lung disease, but not without serious adverse side effects. Gastric perforation is unusual (2%) and it is believed that steroid induced reduction in the prostaglandin mediated protective mechanisms associated with the gastric mucosa allows normal levels of acid secretion to cause erosions, which may lead to perforation. Two possible ways of preventing this are to increase the protective mechanisms or to decrease hydrogen ion secretion. Future developments may include the use of misoprostol an analogue of prostaglandin E_1 , which may prove to be beneficial in protecting the gastric mucosa. Currently, however, increasing the gastric pH to above 4 is known to significantly decrease the risk of damage to the gastric mucosa.¹²

An infusion of 0.0625 mg/kg/hour of ranitidine was sufficient to maintain the gastric pH to above 4 in all of the infants studied. There was no added benefit from having an infusion of 0.125 mg/kg/hour, and a lower rate of 0.031 mg/kg/hour did not achieve sufficient H_2

blockade. Gastric acid is thought to protect the gastrointestinal tract from becoming overgrown with pathogenic organisms and so giving ranitidine could interfere with an important defence mechanism. During this study we noted no gastrointestinal problems in the infants that could be attributed to a change in gut flora.

In order to show that the use of ranitidine significantly reduces the incidence of dexamethasone induced gastric bleeds or perforations a randomised clinical trial involving over 2000 infants would have to be performed. We, therefore, have adopted the pragmatic approach and give all infants treated with dexamethasone an infusion of 0.0625 mg/kg/hour of ranitidine.

H₂ blockers may be used in preterm infants in the management of gastric bleeding due to various factors during intensive care. These data clearly demonstrate that the preterm infant produces low intragastric pH and that H₂ blockade is effective at decreasing intragastric acidity. These data, however, may not translate to the patient who is not receiving steroids and recommendations about the dosage of ranitidine are not yet possible in babies who are not given dexamethasone.

The question of how long any steroid induced decrease in the prostaglandin mediated mucosal protection lasts and whether receptor blockade should continue after steroid treatment remains unanswered. In experimental animals, use of short term H₂ blockade results in up-regulation of H₂ receptors on the parietal cells and an increase in parietal cell mass due to hypergastrinaemia.^{13 14} There is also concern in the adult literature that rapid cessation of H₂ blockade may be associated with reactive hyperacidity,¹⁵ which may precipitate mucosal damage. As we have previously described,² in this centre, a three week tapered dose regimen of dexamethasone is used in the management of infants with BPD. Our current policy is that ranitidine is given continuously throughout the three week period of steroid treatment. In view of the buffering effect of milk, and the putative

mucosal protection provided by epidermal growth factor found in breast milk,¹⁶ ranitidine may be stopped in infants receiving 90 ml/kg of milk feeds during the period of steroids. The timing and mode of cessation of H₂ blocker treatment, however, remains an important area that requires further elucidation.

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- 1 Collaborative Dexamethasone Trial Group. Dexamethasone therapy in neonatal chronic lung disease: an international placebo-controlled trial. *Pediatrics* 1991; **88**: 421-7.
- 2 Ng PC, Brownlee KG, Dear PRF. Gastroduodenal perforation in preterm babies treated with dexamethasone for bronchopulmonary dysplasia. *Arch Dis Child* 1991; **66**: 1164-6.
- 3 O'Neil EA, Chwals WJ, O'Shea MD, Turner CS. Dexamethasone treatment during ventilator dependency: possible life threatening gastrointestinal complications. *Arch Dis Child* 1992; **67**: 10-1.
- 4 Newell SJ, Booth IW, Morgan MEI, Durbin GM, McNeish AS. Gastro-oesophageal reflux in preterm infants. *Arch Dis Child* 1988; **63**: 780-6.
- 5 Herbst JT, Minton SD, Book LS. Gastroesophageal reflux causing respiratory distress and apnea in newborn infants. *J Pediatr* 1979; **95**: 763-8.
- 6 Robertson NRC, ed. *Textbook of neonatology*. Edinburgh: Churchill Livingstone, 1986.
- 7 Sondheimer JM, Clark DA, Gervaise EP. Continuous gastric pH measurement in young and older healthy preterm infants receiving formula and clear liquid feedings. *J Pediatr Gastroenterol Nutr* 1985; **4**: 352-5.
- 8 Lacroix J, Rivard CI, Gauthier M, Rousseau E, Doesburg N. Upper gastrointestinal tract bleeding acquired in a pediatric intensive care unit: prophylaxis trial with cimetidine. *J Pediatr* 1986; **108**: 1015-8.
- 9 Chattriwalla Y, Colon AR, Scanlon JW. The use of cimetidine in the newborn. *Pediatrics* 1980; **65**: 301-2.
- 10 Rosenthal M, Miller PW. Ranitidine in the newborn. *Arch Dis Child* 1989; **64**: 88-9.
- 11 Hyman P, Clarke DD, Everett SL. Gastric and secretory function in preterm infants. *Pediatrics* 1985; **106**: 467-8.
- 12 Walker S, Klotz U, Sarem-Aslani A, Treiber G, Bode JC. Effect of omeprazole on nocturnal intragastric pH in cirrhotics with inadequate antisecretory response to ranitidine. *Digestion* 1991; **48**: 179-84.
- 13 Witzel L, Halter F, Alah AJ, Kacki WH. Effects of prolonged metiamide medication on the fundic mucosa. A secretory and histomorphometric study in the rat. *Gastroenterology* 1977; **73**: 797-803.
- 14 Wilder-Smith C, Halter F, Ernst T, et al. Loss of acid suppression during dosing with H₂-receptor antagonists. *Alimentary Pharmacology and Therapeutics* 1990; **4** suppl 1: 15-28.
- 15 Rogers MJ, Holmfield JHM, Primrose JN, Johnston D. The effects of 15 days of dosing with placebo, sufofodine 600 mg nocte or sufofodine 600 mg twice daily on 24-h intragastric acidity and 24-h plasma gastrin. *Alimentary Pharmacology and Therapeutics* 1990; **4** suppl 1: 65-74.
- 16 Gale SM, Read LC, George-Nascimento C, Wallace JC, Ballard FJ. Is dietary epidermal growth factor absorbed by premature human infants? *Biol Neonate* 1989; **55**: 104-10.