

## Duodenal perforation associated with tolazoline

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**SUMMARY** A neonate, managed with tolazoline for pulmonary hypertension after repair of a congenital diaphragmatic hernia, developed a duodenal perforation. The role of tolazoline in this condition is discussed, and possible measures to reduce its gastrointestinal side effects are proposed.

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Pulmonary hypertension with persistence of fetal circulation is a well recognised complication of congenital diaphragmatic hernia.<sup>1</sup> It can be treated in this and other neonatal conditions by the vasodilator effects of tolazoline. Reported complications of this drug include systemic hypotension, thrombocytopenia, pulmonary haemorrhage, seizures, oliguria, haematuria, hyponatraemia, abdominal distention,<sup>1</sup> and gastrointestinal haemorrhage.<sup>2</sup> We report a rare case of duodenal perforation after the use of tolazoline.

### Case report

A male infant was born by spontaneous vertex delivery at 41 weeks' gestation to a multigravida mother. He weighed 3750 g and immediately developed respiratory distress due to a left diaphragmatic hernia. An x ray film of his chest confirmed the diagnosis, and analysis of capillary blood gases showed a respiratory acidosis (pH 7.05, arterial oxygen tension ( $P_{aO_2}$ )=3.68 kPa, arterial carbon dioxide tension ( $P_{aCO_2}$ )=9.0 kPa, and base deficit=16). Nasogastric and endotracheal tubes were passed, 10 mmol of sodium bicarbonate was administered intravenously, and mechanical ventilation was started at the referring maternity hospital.

After transfer to the neonatal surgical unit his blood gases improved, and operation was undertaken without delay. Through a left subcostal incision the hernia contents of stomach, spleen, small bowel, and proximal large bowel were removed from the chest; the sac was excised; and the large posterolateral diaphragmatic defect was repaired. The left lung was hypoplastic, occupying only the apex of the left thorax. Bilateral chest drains were inserted, and mechanical ventilation was continued postoperatively. Initial blood gases were normal with  $F_{IO_2}$  of 0.4.

Thirty hours postoperatively a fall in transcutaneous  $P_{aO_2}$  was noted, and this trend continued despite increased  $F_{IO_2}$  to 1 and a rate of ventilation of 30/minute. Entry of air was satisfactory and an x ray film of his chest confirmed that both lungs were expanded. Capillary blood gases indicated progressive hypoxaemia (pH 7.18,  $P_{aO_2}$ =2.37 kPa,  $P_{aCO_2}$ =5.65 kPa, and base deficit=3). Pulmonary hypertension was suspected, and accordingly the infant was paralysed with pancuronium and hyperventilated at 50 per minute with  $F_{IO_2}$ =1 (inspiratory pressure 18 mm Hg, positive end expiratory pressure 2 mm Hg, 0.5 seconds inspiration/0.7 seconds expiration).

After two hours of hyperventilation there was little improvement in transcutaneous  $P_{aO_2}$  or capillary blood gases (pH 7.29,  $P_{aO_2}$ =3.2,  $P_{aCO_2}$ =6.7, and base deficit=2). Tolazoline was therefore given into a vein in the scalp as a bolus of 2 mg/kg and continued at 2 mg/kg/hour by infusion. By this regimen the infant's capillary blood gases improved rapidly (pH 7.56,  $P_{aO_2}$ =6.3,  $P_{aCO_2}$ =5.1, and base deficit=-6).

Forty eight hours after starting treatment with tolazoline the blood gases were stable and the drug dosage and  $F_{IO_2}$  were gradually reduced. Twelve hours later nasogastric aspirates were positive for blood and a small amount of blood was passed rectally; there was no associated thrombocytopenia (platelet count  $210 \times 10^9/l$ ). Abdominal distension became obvious and a plain x ray film confirmed the presence of free intraperitoneal gas. At laparotomy a perforation of the first part of the duodenum was found and repaired. In the absence of any apparent local cause (the nasogastric tube was high in the stomach) the perforation was presumed to be related to increased secretion of gastric acid secondary to tolazoline.

### Discussion

Tolazoline has been used in the treatment of pulmonary hypertension in neonates.<sup>1</sup> It is classified pharmacologically as an alpha adrenergic blocking agent but has other actions that are probably more important clinically.

The vasodilator action on the pulmonary circulation is mediated via histamine receptors.<sup>3</sup> Stimula-

tion of gastric H<sub>2</sub> receptors, producing increased gastric secretion, may account for the unwanted gastrointestinal side effects. Stevens *et al* found increased gastric aspirate in 36% of 47 neonates treated with tolazoline and a haematest positive aspirate in 55%.<sup>1</sup> Dillard reported a fatal episode of haemorrhage from acute gastric erosions.<sup>2</sup> Duodenal perforation in association with tolazoline has only once been previously recorded.<sup>4</sup>

Drummond *et al* showed that hyperventilation with induced respiratory alkalosis is effective in correcting right to left shunting in persistent pulmonary hypertension.<sup>5</sup> In our patient improvement occurred only after treatment with tolazoline was combined with hyperventilation. In view of the potential hazards of tolazoline, however, we would continue to reserve its use for failure of a regimen of muscular paralysis and hyperventilation alone.

In this infant the standard recommended dose was used, but recent work on the pharmacokinetics of tolazoline suggests that this is too high as the long half life may lead to toxic accumulation.<sup>6</sup> This may account for the commonly observed cardiovascular side effects. Initial studies suggest that there is no pharmacokinetic justification for continuous infusion of tolazoline, particularly in the presence of oliguria. Our patient had normal renal function, but the perforation occurred despite reduction of the dosage to 0.5 mg/kg/hour 12 hours previously. Microassay of serum concentrations has been developed and should result in more rational use of

tolazoline with a consequent decrease in dose related side effects.

If tolazoline is used, the monitoring of gastric secretion by nasogastric aspiration and pH measurements would be worthwhile. Perforation in our patient was preceded by a nasogastric aspirate of 120 ml in 24 hours, with blood detected latterly. Theoretically, H<sub>2</sub> antagonists such as cimetidine will inhibit not only the undesirable gastric side effects of tolazoline but also its therapeutic action, thus the use of simple prophylactic antacids may be a better option in infants requiring tolazoline.

#### References

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