

MIDAZOLAM (Commentary)

Comments on the safety of neonatal use

Attention needs to be drawn to the result of one recent small randomised controlled trial comparing the use of midazolam, morphine and a 'placebo' glucose solution in 67 preterm babies of 24-32 weeks gestation who were not perceived to be in overt pain but were judged to merit sedation while ventilated for respiratory distress (Anand *et al.* 1999). Sedation in this pilot study (the NOPAIN trial) was given for a median of five days using a loading dose and a maintenance infusion not radically different from the one outlined in this Formulary. The babies given midazolam or morphine appeared to be more sedated than the placebo group as assessed using the COMFORT score (Ambuel *et al.* 1992). However there was a statistically significant higher incidence of adverse neurological events (death, grade III-IV intraventricular haemorrhage or periventricular leukomalacia) in the midazolam group compared with the other groups. While this may have been a chance finding in a small trial, a decision was taken, when these findings became available, to exclude any further study of this drug during the larger NEOPAIN trial (Anand *et al.*, 2004).

The widespread use of a continuous midazolam infusion remains one of a large number of neonatal treatment strategies that have come into widespread use over the last fifteen years without ever undergoing rigorous evaluation. While the unexpected adverse outcome uncovered by the NOPAIN study could well have arisen by chance despite its 'statistical significance' because of the trial's small size, the finding should, as a minimum, point to the danger of taking such a technique into routine use until further studies have been conducted (Ambalayanan and Carb, 1999). It is also important to bear in mind (as the American Academy of Pediatrics stresses) that benzodiazepines do not provide pain relief. The most recent Cochrane review has certainly concluded, after analysing the outcome of the NOPAIN trial and the earlier trial reported by Jacqz-Aigrain in 1994, that there is "insufficient evidence to promote the use of intravenous midazolam infusion as a sedative for neonates undergoing intensive care."

Ambuel B, Hamlett KW, Marx CM, *et al.* Assessing distress in pediatric intensive care environments: the COMFORT scale. *J Pediatr Psychol* 1992;**17**:95-109.

Anand KJS, McIntosh N, Lagercrantz H, *et al.* Analgesia and sedation in preterm neonates who require ventilatory support - results from the NOPAIN trial. *Arch Pediatr Adolesc Med* 1999;**153**:331-8. [RCT].

Ambalayanan N, Carlo WA. Analgesia for ventilated neonates: where do we stand? [Editorial] *J Pediatr* 1999;**135**:403-5.

American Academy of Pediatrics. Prevention and management of pain and stress in the neonate. *Pediatrics* 2000;**105**:454-61.

Ng E, Taddio A, Ohlsson A. Intravenous midazolam infusion for sedation of infants in the intensive care unit. *The Cochrane Library*. Oxford: Update Software, 2000. [SR]

Anand KJS, Whit Hall R, Desai N, *et al.* Effects of morphine analgesia in ventilated preterm neonates: primary outcomes from the NEOPAIN randomised trial. *Lancet* 2004;**363**:2673-82. (See also **364**:498.) [RCT]

Other References

Silvasi DL, Rosen DA, Rosen KR. Continuous intravenous midazolam infusion for sedation in the pediatric intensive care unit. *Anesth Analg* 1986;**67**:286-8.

Jacqz-Aigrain E, Wood C, Robieux I. Pharmacokinetics of midazolam in critically ill neonates. *Eur J Pharmacol* 1990;**30**:191-2.

Hartwig S, Roth B, Theisohn ML. Clinical experience with continuous intravenous sedation using midazolam and fentanyl in the pediatric intensive care unit. *Eur J Pediatr* 1991;**150**:784-8.

Burtin P, Daoud P, Jacqz-Aigrain E, *et al.* Hypotension with midazolam and fentanyl in the newborn. *Lancet* 1991;**337**:1545-6.

Ambuel B, Hamlett KW, Marx CM, *et al.* Assessing distress in pediatric intensive care environments: the COMFORT scale. *J Pediatr Psychol* 1992;**17**:95-109.

van den Anker JN, Sauer PJJ. The use of midazolam in the preterm neonate [letter]. *Eur J Pediatr* 1992;**151**:152.

van Straaten HLM, Rademaker CMA, de Vries LS. Comparison of the effect of midazolam or vecuronium on blood pressure and cerebral blood flow velocity in the premature newborn. *Dev Pharmacol Ther* 1992;**19**:191-5.

Jacqz-Aigrain E, Daoud P, Burtin P, *et al.* Placebo-controlled trial of midazolam sedation in mechanically ventilated newborn babies. *Lancet* 1994;**344**:646-50. [RCT]

Burtin P, Jacqz-Aigrain E, Girard P, *et al.* Population pharmacokinetics of midazolam in neonates. *Clin Pharmacol Ther* 1994;**56**:615-25.

Magny JF, d'Allest AM, Nedelcoux H *et al.* Midazolam and myoclonus in neonate. *Eur J Pediatr* 1994;**153**:389-90.

Ducharme MP, Munzenberger P. Severe withdrawal syndrome possibly associated with cessation of a midazolam and fentanyl infusion. *Pharmacotherapy* 1995;**15**:665-8.

Olkola KT, Ahonen J, Neuvonen PJ. The effect of the systemic antimycotics, itraconazole and fluconazole, on the pharmacokinetics and pharmacodynamics of intravenous and oral midazolam. *Anesth Analg* 1996;**82**:511-6.

Jacqz-Aigrain E, Burtin P. Clinical pharmacokinetics of sedatives in neonates. *Clin Pharmacokinet* 1996;**31**:423-43.

McCarver-May DG, Kang J, Aouthmany M, *et al.* Comparison of chloral hydrate and midazolam for sedation of neonates for neuroimaging studies. *J Pediatr* 1996;**128**:573-6. [RCT]

O'Reagan ME, Brown JK, Clarke M. Nasal rather than rectal benzodiazepines in the management of acute childhood seizures? *Dev Med Child Neurol* 1996;**38**:1037-45. (See also 1997;**37**:137-8.)

- Hughes J, Gill AM, Mulhearn H, *et al.* Steady-state plasma concentrations of midazolam in critically ill infants and children. *Ann Pharmacother* 1996;**30**:27–30.
- Sheth RD, Buckley DJ, Gutierrez AR, *et al.* Midazolam in the treatment of refractory neonatal seizures. *Clin Neuropharmacol* 1996;**2**:165–70.
- Harte GJ, Gray PH, Lee TC, *et al.* Haemodynamic responses and population pharmacokinetics of midazolam following administration to ventilated, preterm neonates. *J Paediatr Child Health* 1997;**33**:335–8.
- Massanari M, Novitsky J, Reinstein LJ. Paradoxical reactions in children associated with midazolam use during endoscopy. *Clin Pediatr* 1997;**36**:681–4.
- Geldner G, Hubmann M, Kroll R, *et al.* Comparison between three transmucosal routes of administration of midazolam in children. *Pediatr Anaesth* 1997;**7**:103–9.
- Scott RC, Beaag FMC, Boyd SG, *et al.* Buccal absorption of midazolam: pharmacokinetics and EEG. *Pharmacol Ther* 1999;**70**:525–31.
- Waisman D, Weintraub Z, Rotschild A, *et al.* Myoclonic movements in very-low-birth-weight premature infants associated with midazolam intravenous bolus administration. [Letter] *Pediatrics* 1999;**104**:579.
- Attardi DM, Paul DA, Tuttle DJ, *et al.* Endotracheal intubation in awake versus sedated premature infants: a randomised double blind placebo-controlled trial [Abstract]. *Pediatr Res* 1999;**45**:183A. [RCT]
- Anand KJS, McIntosh N, Lagercrantz H, *et al.* Analgesia and sedation in preterm neonates who require ventilatory support – results from the NOPAIN trial. *Arch Pediatr Adolesc Med* 1999;**153**:331–8. [RCT]
- Ambalavanan N, Carlo WA. Analgesia for ventilated neonates: where do we stand? [Editorial] *J Pediatr* 1999;**135**:403–5.
- Lee TC, Charles BG, Harte GJ, *et al.* Population pharmacokinetic modeling in very premature infants receiving midazolam during mechanical ventilation. *Anesthesiology* 1999;**90**:451–7.
- Birrell VL, Wyllie JP, Pagan J. Midazolam causing convulsions. *Br J Int Care* 1999;197.
- de Wildt SN, Kearns GL, Hop WCJ, *et al.* Pharmacokinetics and metabolism of intravenous midazolam in preterm infants. *Clin Pharmacol Ther* 2001;**70**:525–31.
- Zaw W, Knoppert DC de Silva O. Flumazenil's reversal of myoclonic-like movements associated with midazolam in term newborns. *Pharmacotherapy* 2001;**21**:642–6.
- de Wildt SN, Kearns GL, Hop WCJ, *et al.* Pharmacokinetics and metabolism of oral midazolam in preterm infants. *Br J Clin Pharmacol* 2002;**53**:390–2.

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Availability of a product suitable for nasal or buccal administration

Special Products in the UK have a “named patient” formulation available that parents can use to control seizures. Parents should be told that, if any fit last longer than five minutes, they can give 0.03 ml/kg of this sugar-free liquid into the side of the mouth (between the cheek and the lower teeth). Half the dose should be given into each side of the mouth if possible. A second dose can be given after 10 minutes if the seizure persists. The dose can, alternatively, be given into the back of the nose, especially if the child is salivating excessively. Cartons contain four 1-ml oral syringes and 5 ml of sugar-free liquid containing 10 mg/ml of midazolam in an amber glass bottle suitable for home use. The bottle’s child resistant closure **must** be sealed again promptly after use to prevent excess evaporation. Cartons cost £14 each.

- Scott RC, Besag FM, Neville BG. Buccal midazolam and rectal diazepam for treatment of prolonged seizures in childhood and adolescence: a randomised trial. *Lancet* 1999;**353**:623–6. (See also 608-9.) [RCT]
- Lahat E, Goldman M, Barr J, *et al.* Comparison of intranasal midazolam with intravenous diazepam for treating febrile seizures in children: prospective randomised study. *BMJ* 2000;**321**:83–6. [RCT]
- Rainbow J, Browns GJ, Lam LT. Controlling seizures in the prehospital setting: diazepam or midazolam? *J Paediatr Child Health* 2002;**38**:582–6.
- McIntyre J, Robertson S, Norris E, *et al.* Safety and efficacy of buccal midazolam versus rectal diazepam for emergency treatment of seizures in children: a randomised controlled trial. *Lancet* 2005;**366**:205–10. (See also 182–3.) [RCT]