MIDAZOLAM (Commentary)

Sustained sedation in neonates needing intensive care

A small but important randomised controlled trial (the NOPAIN trial) in 1999 compared 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. Sedation in this pilot study was given for a median of five days (Anand *et al,.* 1999) using a loading dose and a maintenance infusion not very 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 then in 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 midazolam was one of a number of treatment strategies that came into widespread use in paediatric and then neonatal intensive care during the 1990s 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 Cochrane review concluded in 2003, after analysing the outcome of the only three trials done to date, that there was "insufficient evidence to promote the use of intravenous midazolam infusion as a sedative for neonates undergoing intensive care" and "this review raises questions about the safety of midazolam in neonates" (Ng *et al.,* 2003). No further studies have been done since then. Since benzodiazepines do not provide pain relief (as the report by the American Academy of Pediatrics stressed in 2000), and since sustained use commonly causes quite unpleasant withdrawal symptoms in older children (in whom the existence of such adverse effects is probably easier to assess), the drug's continued use as a neonatal sedative is hard to justify. Gestation has a marked effect on the drug's half life, and clearance changes fairly rapidly during the first few weeks of life. The drug's variable pharmacokinetics and pharmacodynamics (see below) poses a challenge to the effective use of this drug in children too young for distress to be assessed with ease. The way in which gestation affects the drug's half life, and the way in which clearance increases during the first weeks and months of life makes it even harder to judge the efficacy of sustained use in very young children.

Silvasi DL, Rosen DA, Rosen KR. Continuous intravenous midazolam infusion for sedation in the pediatric intensive care unit. *Anesth Analg* 1986;**67**:286–8. Booke PD, Beechey A, Lloyd-Thomas AR. Sedation of children requiring artificial ventilation using an infusion of midazolam. *Br J Anaesth* 1986;**58**:1104–8.Silvasi DL, Rosen DA, Rosen KP. Continuous intravenous midazolam infusion for sedation in the pediatric intensive care unit. *Anesth Analg* 1988;**67**:286–8

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.

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]

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.

American Academy of Pediatrics. Canadian Paediatric Society. Prevention and management of pain and stress in the neonate. *Pediatrics* 2000;**105**:31–8.

Arya V, Ramji S. Midazolam sedation in mechanically ventilated newborns: double blind randomized placebo controlled trial. *Indian Pediatr* 2001;**38**:967–72. [RCT]

Ng E, Taddio A, Ohlsson A, Intravenous midazolam infusion for sedation of infants in the neonatal intensive care unit. *Cochrane Database of Systematic Reviews* 2003 Issue 1. Art No.:CD002052.

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]

Anand KJS. Pharmacological approaches to the management of pain in the neonatal intensive care unit. [Review} *J Perinatol* 2007;**27**:S4–11.

Menon G, McIntosh N. How should we manage pain in ventilated neonates? [Review] *Neonatology* 2008;**93**:316–23.

Carbajal R, Rousset A, Danan C, *et al.* Epidemiology and treatment of painful procedures in neonates in intensive care units. *JAMA* 2008;**300**:60–70.

Pharmacokinetics in early infancy

Gestation has a marked effect on the drug's half life, and clearance changes fairly rapidly during the first few weeks of life. The drug's variable pharmacokinetics and pharmacodynamics (de Wildt *et al,* 2005; Peeters *et al.,* 2006) poses a further challenge to effective use in children too young for distress to be assessed with ease.

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

Jacqz-Aigrain E, Daoud P, Burtin P, *et al.* Pharmacokinetics of midazolam during continuous infusion in critically ill neonates. *Eur J Clin Pharmacol* 1992;**42**:329.

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

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

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.

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.

Blumer JL. Clinical pharmacology of midazolam in infants and children. *Clin Pharmacokinet* 1998;**35**:37–47.

Lee TC, Charles BG, Harte GJ, *et al.* Population pharmacokinetic modelling in very premature infants receiving midazolam during mechanical ventilation. *Anesthesiology* 1999;**90**:451–7.

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.

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.

Treluyer JM, Zohar S, Rey E, *et al.* Minimum effective dose of midazolam for sedation of mechanically ventilated neonates. *J Clin Pharm Ther* 2005;**30**:479–85.

de Wildt SN, de Hoog M, Vinks AA, *et al.* Pharmacodynamics of midazolam in pediatric intensive care patients. *Ther Drug Monit* 2005;**27**:98–102.

Peeters MYM, Prins SA, Knibbe CAJ, *et al.* Pharmacokinetics and pharmacodynamics of midazolam and metabolites in nonventilated infants after craniofacial surgery. *Anesthesioloigy* 2006;**105**:1135–46.

Risk of withdrawal symptoms after sustained use

There have been several reports that use can cause hypotension (especially when the first 'loading 'dose is given) and that use can sometimes trigger myoclonic movements, and it is now also widely accepted that distressing withdrawal symptoms are not uncommon with sustained use. In a careful prospective study involving older children as well as neonates (Ista *et al.,* 2008) anxiety, agitation, sleeplessness, increased muscle tone, fever, sweating, tachypnoea and diarrhoea were the problems most commonly encountered. The higher the dose use and the longer the treatment was sustained the more serious and distressing the withdrawal symptoms became.

Bergman I, Steeves M, Buckart G, *et al.* Reversible neurologic abnormalities associated with prolonged intravenous midazolam and fentanyl administration. *J Pediatr* 1991; **119**: 644–9.

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.

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.

Magnyn 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.

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.

Birrell VL, Wyllie JP, Pagan J. Midazolam causing convulsions. *Br J Int Care* 1999:197.

Fonsmark L. Rasmussen Y, Carl P. Occurrence of withdrawal in critically ill sedated children. *Crit Care Med* 1999;**27**:196–9.

Ista E, van Diik M, Gamei C, et al. Withdrawal symptoms in critically ill children after long term administration of sedatives and or analgesics: a first evaluation. *Crit Care Med* 2008;**36**:2427–32.

Availability of a product suitable for nasal or buccal administration

There is now a widespread acceptance that midazolam is very rapidly absorbed through mucosal skin. and that a 'stat' dose of midazolam given into the nose or mouth and held there unswallowed ('buccal' administration) is both the quickest and most effective way of bringing sustained seizure activity to a halt. Blood levels rise rapidly, and placing a dose 'under the tongue' works more reliably and more quickly than giving a dose into the rectum. Such an approach is also much less distressing to all concerned. The generally accepted dose for stopping seizure activity seems to be 300 micrograms/kg, but a dose of 400 or even 500 micrograms/kg actually seems to be entirely safe, and may be preferable since the sooner the 'rescue' drug is given the more effective it seems to be. Something can now be done before the child reaches hospital and, even in hospital, the "search for a suitable vein" looses its urgency.

It is generally said that the initial dose can be repeated after 10 minutes if seizures continue and that a total buccal dose of 1mg/kg is *usually* safe. However, because of the risk of respiratory depression, a total dose this high should probably only be given by someone competent in providing sustained respiratory support (as some ambulance staff and paramedics now are in the UK). The fact that even a dose this high may not control seizure activity in many children with cerebral malaria is not, in itself, a good reason to modify this guidance. The unintended administration of too high a dose by *any* route is, of course, potentially dangerous, and a spate of such cases has led some hospitals in the UK to insist that wards only stock ampoules of one strength.

Special Products in the UK already have a "named patient" formulation available that parents can use to control seizures. Parents are generally told that, if any fit lasts 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). It is generally said that half the dose should be given into each side of the mouth if possible, and it is easy to see why this might be true. However, there is very little good evidence that it really matters, and stressing this only serves to increase the pressure on an already anxious parent or teacher. 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.

It is greatly to be hoped that a single, fixed-dose, buccal product may become available on the UK market shortly. If it were to become available this would make parents, nurses and school staff much less reluctant to use this way of bringing sustained, and understandably distressing, seizure activity to a halt. A device for giving graded doses as a nasal spray has been described ((Ljungman *et al.,* 2000) but it does not seem to be commercially available as yet. Too many young children with epilepsy are, for all practical purposes, 'therapeutic orphans' at the moment.

Karl HW, Rosenberger JL, Larach MG, *et al.* Transmucosal administration of midazolam for premedication in pediatric patients. Comparison of the nasal and sublingual routes. *Anesthesiology* 1993;**78**:885–91. [RCT]

Malinovsky JM, Populairie G, Cozain A, *et al.* Premedication with midazolam in children: effect of intranasal, rectal and oral routes on plasma midazolam concentrations. *Anesthesia* 1995;**50**:351–4.

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

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, Besag FM, Neville BG. Buccal midazolam and rectal diazepam fir treatment of prolonged seizures in childhood and adolescence: a randomised trial. *Lancet* 1999;**353**:623–6. (See also 608-9.) [RCT]

Ljungman G, Kreuger A, Andreasson S, *et al.* Midazolam nasal spray reduces procedural anxiety in children. *Pediatrics* 2000;**105**:73–8.

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.

Baysun S, Aydin OF, Atmaca E, *et al.* A comparison of buccal midazolam and rectal diazepam for the acute treatment of seizures. *Clin Pediatr Phila* 2005;**44**:771–6.

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]

Kyroou M, Harbord M, Kyrkou N, *et al.* Community use of intranasal midazolam for managing prolonged seizures. *J Intellect Dev Disabil* 2006;**31**:131–8.

Bhattacharyya M, Kaira V, Gulati S. Intranasal midazolam vs rectal diazepam in acute childhood seizures. *Pediatr Neurol* 2006;**34**:355–9.

Holsti M, Sili BL, Firth SD, *et al.* Prehospital intranasal midazolam for the treatment of pediatric seizures. *Pediatr Emerg Care* 2007;**23**:148–53.

Muchohi M, Kokwaro GO, Oquto BR, *et al.* Pharmacokinetics and clinical efficacy of midazolam in children with severe malaria and convulsions. *Br J Clin Pharmacol* 2008;**66**:529–38.

Mpimbaza A, Ndeezi G, Staedke S, *et al.* Comparison of buccal midazolam with rectal diazepam in the treatment of prolonged seizures in Ugandan children: a randomized clinical trial. *Pediatrics* 2008;**121**:e58–64. [RCT]

Use to control persistent seizures

Although the sustained neonatal use of midazolam as a sedative has declined since the outcome of the trials by Jacqz-Aigrain *et al.* and by Anand *et al.* were published in 1994 and 1999, and the frequency with which withdrawal symptoms are seen after sustained use has became more widely recognised, there *has* been sustained interest in the drug's use as an anticonvulsant when first line treatment proves ineffective. Several papers have appeared confirming that midazolam does usually bring such seizures under control (as it certainly does in older children), although there have been no satisfactory head-to-head comparisons as yet, and a single 'stat' dose of lorazepam (q.v.) may turn out to be the best benzodiazepine to use – management is certainly made simpler if the drug chosen does not need to be given as a slow sustained infusion. The only non-random study published to date suggests that lidocaine (q.v.) may be marginally more effective than midazolam (Shany *et al.,* 2007), and this is what Boylan also found in 2004.

Rivera R, Sengini M, Baltofano A, *et al.* Midazolam for the treatment of status epilepticus in children. *Crit Care Med* 1993;**21**:991–4.

Sheth RD, Buckley DJ, Gutierrez AR, *et al.* Midazolam in the treatment of refractory neonatal seizures. *Clin Neuropharmacol* 1996;**2**:165–70.

Mingagawa K, Yanai S. Efficacy of intravenous infusion of midazolam in the treatment of statues epilepticus in children. *No To Hattatsu* 1998;**30**:290–4.

van Leuven K, Groenendaal F, Toet MC, *et al.* Midazolam and amplitude-integrated EEG in asphyxiated full-term neonates. *Acta Paediatr* 2004;**93**:1221–7. (See also 1153–4.)

Boylan GB, Rennie JM, Chorley G, *et al.* Second-line anticonvulsant treatment of neonatal seizures: a video-EEG monitoring study. *Neurology* 2004;**62**:486–8. [RCT]

Ozdemir D, Gulez P, Uran N, *et al.* Efficacy of continuous midazolam infusion and mortality in childhood refractory generalised convulsive status epilepticus. *Seizure* 2005;**14**:129–32.

Casto Conde JR, Hermandez Borges AA, Martinez E, *et al.* Midazolam in neonatal seizures with no response to phenobarbital. *Neurology* 2005;**64**:876–9.

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]

Morrison G, Gibbons E, Whitehouse WP. High-dose midazolam therapy for refractory status epilepticus in children. *Intensive Care Med* 2006;**32**:2070–6..

Mital P, Manohar R, Rawat AK. Comparative study of intranasal midazolam and intravenous diazepam sedation for procedures and seizures. *Indian J Pediatr* 2006;**73**:975–8. [RCT]

Hayashi K, Osawa M, Aishara M, *et al.* Efficacy of intravenous midazolam for status epilepticus in childhood. *Pediatr Neurol* 2007;**36**:366–72.

Shany E, Benzaqen O, Watemberg N. Comparison of continuous drip of midazolam or lidocaine in the treatment of intractable neonatal seizures. *J Child Neurol* 2007;**22**:255–9.

Papavasiliou AS, Kotsalis C, Paraskevoulakos E, *et al.* Intravenous midazolam in convulsive status epilepticus in children with pharmacoresistant epilepsy. *Epilepsy Behav* 2009;**14**:661–4.

Use as a short-term procedural sedative

A single 200 microgram/kg dose given IV produced enough sedation to make computed tomography possible in most children in one recent large study (Singh *et al.,* 2009) although a few babies required twice as much as this. These children (6 months to 6 years old) were monitored using a pulse oximeter, but only 7% were judged to need supplemental oxygen because of marginal desaturation (a SpO_2 of 90–95%). A 300 microgram/kg dose under the tongue was enough to make echocardiography possible in one recent study (Layangool *et al.,* 2008). A 200 or 300 microgram/kg dose into the nose was enough to make ophthalmic examination relatively easy in a second recent study in children who were 6 to 26 months old (Altintas *et al.,* 2005), and a 400 microgram/kg dose into the nose was enough to facilitate most procedures, including the suturing of cuts and lacerations in a third recent study in children 1 to 60 months old (Lane and Schunk, 2008). Adverse events were almost non-existent in these four studies.

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]

Altintas O, Karabas VL, Demirci G, *et al.* Evaluation of intranasal midazolam in refraction and fundus examination of young childrenwith strabismus. *J Pediatr Ophthalmol Strabismus*. 2005;**42**:355–9.

Lane RD, Schunk JE. Atomized intranasal midazolam use for minor procedures in the pediatric emergency department. *Pediatr Emerg Care* 2008;**24**:300–3.

Layangool T, SangtawesinC, Kirawittaya T, *et al.* A comparison of chloral hydrate and sublingual midazolam sedation for echocardiogram in children. *J Med Assoc Thai* 2008;**91** Suppl 3:S45–52. [RCT]

Singh R, Kumar N, Vajifdar V. Midazolam as a sole sedative for computed tomography imaging in pediatric patients. *Pediatr Anaesth* 2009;**19**:899–904.

Use of flumazenil

Flumazenil is a benzodiazepine antagonist that can be used to reverse any unwanted effects of benzodiazepine sedation. If one of two 10 microgram/kg doses do not result in the child becoming more alert the child's drowsiness is unlikely to be due to midazolam. The half life of flumazenil is much shorter than that of midazolam, so further doses will be necessary to sustain any beneficial effect achieved. Flumazenil has also been used with apparent success to control the paradoxical reactions sometimes encountered when midazolam is used (Massanari *et al.,* 1997).

Massanari M, Novitsky J, Reinstein LJ. Paradoxical reactions in children associated with midazolam use during endoscopy. *Clin Pediatr* 1997;**36**:681–4.

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.

Aviram EE, Ben-Abraham R, Weinbrioum AA. Flumazenil use in children. *Paed Perinatal Drug Ther* 2004;**5**:202–9.

Maternal use

There is nothing to suggest that midazolam is teratogenic in animals. There do not seem to be any formal studies of its use in the first two trimesters of human pregnancy. Its use prior to caesarean delivery only seems to cause very slight neonatal sedation. Brief use during lactation only results in the transfer of trace quantities into the mother's milk.

Crawford ME, Carl P, Bach V, *et al.* A randomized comparison between midazolam and thiopental for elective caesarean section anesthesia. I. Mothers. *Anesth Analg* 1989;**58**:229–33. (See also 234–7.) [RCT]

Matheson I, Lunde PKM, Bredesen JE. Midazolam and nitrazepam in the maternity ward: milk concentrations and clinical effects. *Br J Clin Pharmacol* 1990;**30**:787–93.

Frölish MA, Burchfield DJ, Euliano TY, *et al.* A single dose of fentanyl and midazolam prior to Cesarean section have no adverse neonatal effects. *Can J Anaesth* 2006;**53**:79–85. [RCT]

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