MORPHINE (Commentary)

Attitudes to opiate use in the neonatal period

Intensive care can be a painful business. Nurses have never blinded themselves to this, but it was, until the early 1980s, a reality that doctors found difficult to confront. Local pain could be controlled by local analgesia, but generalised pain was more difficult to contain. Paracetamol (q.v.) can be of help in certain situations but, even in a verbal child, it has proved difficult to establish just how good it is at easing immediate postoperative pain. It does not do much to counteract serious pain. Here there is still no substitute for opiate analgesia. Unfortunately all the opiate drugs can, on occasion, cause serious respiratory depression. As a result doctors tended to ignore the whole issue of pain relief until such time as they became confident enough to say "this child needs morphine so, in order to be sure of giving an adequate dose, I will provide artificial respiratory support."

Even now, after nearly 30 years of study, it is still difficult to be sure what the right dose is. One problem is that the rate at which young babies 'clear' morphine from the body is ***very*** variable – and only influenced to a limited extent by gestational (post-menstrual) and postnatal age. A second problem is that the neonate seems to need a higher blood morphine level than older children and adults to obtain a comparable degree of pain relief. Only one small study has attempted to look at this in any detail (Chay *et al.* 1992). It would be useful to have the findings independently confirmed, but there is much other anecdotal evidence to suggest that this is true. Part of the difference may be that levels of the liver metabolite morphine-6-glucuronide (which is a potent analgesic in its own right) are low in the neonatal period, especially in the first 2–3 days of treatment. Luckily extra corporeal membrane oxygenation (ECMO) treatment does not alter the drug's half life, or the dose needed (Geiduschek *et al,* 1997).

As a result the dose needed to provide pain relief almost certainly affects bladder tone and reduces gut motility, as well as causing a variable and unpredictable degree of respiratory depression. A fixed-dose strategy may be enough to provide sedation and some degree of analgesia for most babies requiring ventilation in the neonatal period. However, all the evidence is that, to optimise relief in any baby experiencing serious sustained pain, treatment ***must*** be individualised and prescribed in a way that leaves the nursing staff with some flexibility over the dose actually given.

Managing the ventilator-dependent baby: The results of the large international NEOPAIN trial (Anand *et al.*, 2004), published in the *Lancet* in June 2004, have shown us that we know less about how to manage sedation and pain relief in the ventilator dependent baby than we thought. The whole process of tracheal intubation must be extremely stressful and unpleasant, and merit the administration of some form of analgesia. There are several alternatives to morphine with a much shorter half life but, where a decision has already been taken to offer sustained respiratory support after intubation, the long half life of morphine may well have the advantage of helping to 'settle' the baby onto such support. While there will be unpredictable emergencies that preclude the prior use of any such 'premedication', such an event should be uncommon in a well managed unit.

It is much less clear whether most babies require continuing sedation or analgesia as a routine once they have been stabilised (Menon and McIntosh, 2008). Most units do not sedate babies being managed with nasal CPAP (Constant Positive Airway Pressure), partly because of the concern to avoid respiratory depression, and many of these babies must suffer almost as much pain and discomfort as a baby of full respiratory support. The tools that have been developed for putting a numerical value to the response of an unintubated baby to acute pain, seem poorly suited to assessing the more chronic stress and discomfort suffered by the intubated baby.

A continuing infusion of 10 micrograms/kg of morphine per hour will serve to calm and sedate most babies, and encourage more to synchronise their own breathing with that of the ventilator (as the controlled trial by Dyke showed in 1995), but staff should not imagine that this does very much to relieve the acute brief pain causing by needles and bloodletting, as those involved in the NOPAIN trial showed (Carbajal *et al.*, 2005). They also found that routine sedation failed to reduce the number of babies judged, by the nurse caring for the baby, to need for further bolus doses of morphine even in babies given three times as much 'base line' morphine as this per hour. The conclusion has to be that it is much more difficult to recognise pain in the intubated baby than is generally recognised, and quite difficult to distinguish restlessness from true distress.

Anyone tempted to 'hedge their bets' and give morphine from a concern that the baby they are caring for is suffering unrecognised pain also needs to be reminded that there was even a suggestion that the routine use of more than a 10 microgram/kg per hour infusion *might* be detrimental in babies of less than 30 weeks gestation. Babies offered sustained morphine certainly took longer to come off respiratory support, and a little longer to tolerate full enteral feeds (Menon *et al.,* 2008). Further analysis of data from the NEOPAIN trial (Hall *et al.*, 2005) showed a link between morphine use and some degree of hypotension, but although "severe IVH, any IVH, and death were associated with pre-existing hypotension" there was no evidence that morphine therapy contributed to those outcomes, and Simons *et al.* 2005, in their analysis of similar data,

also failed to find any evidence to suggest that morphine was causing significant symptomatic hypotension. It is important to remember that pain can cause blood pressure to rise, so a modest fall may simply be a sign that morphine has now brought pain back under control.

Tracheal suction is often thought to be a very distressing procedure, but it is not something for which it is commonly thought appropriate to offer sedation or analgesia in a tracheostomised child. It was the standard stimulus used to assess pain in the NEOPAIN trial, and morphine did nothing to reduce the vigour with which babies responded to suctioning in that trial. Neither however did a 2 mg/kg bolus of ketamine modify the response to suctioning in another small trial recently (Sarrenmaa *et al.*, 2001). Perhaps much of what is seen here is annoyance and an almost reflex response to the sensation that there is 'foreign matter' in the lower airway, and not necessarily a sign of true pain at all. It seems more than possible that the only thing that is ever going to stop the baby objecting to deep suction is moderately deep anaesthesia (not any form of analgesia). The best that can be said for continuous routine opioid sedation for babies needing respiratory support is that it marginally reduces plasma noradrenaline (but not adrenaline) levels (Simons *et al.,* 2005).

The NEOPAIN trial has many strengths, but it needs to be noted that the trial did not attempt to document hypotension directly – a baby was judged to have been hypotensive "if intravenous vasopressors or fluid boluses were administered before or during the first day (or the first three days) of the study drug infusion." Similarly, it was not judged feasible to attempt long term follow-up, so all babies developing Grade III or Grade IV haemorrhage (Papille et al. 1978) or "Cystic echolucency adjacent to the lateral ventricles" (Ment *et al*, 2002) on scans done 4-7 and 28-35 days after birth were treated as having an adverse outcome, even though we know these features do not always consistently predict long term disability.

Managing severe pain: Restlessness in a ventilated baby on a sedative dose of morphine is often simply a sign that the baby is unhappy with the support being offered. The settings may be inappropriate, the tube may be becoming blocked, or a pneumothorax may be developing. Such a baby calls for careful review before sedation is increased.

If, however, it becomes clear that pain is the problem then senior nursing staff ***must*** have the discretion to offer further relief on their own initiative. The longer pain is allowed to continue uncontrolled the harder it becomes to regain control. This is the whole basis of "as needed" (that is "prn" or *"pro re nata"*) prescribing, the guiding principle behind patient-controlled analgesia, and the reason for encouraging experienced midwives to 'top up' an established epidural during childbirth. There are also situations where enhanced analgesia should be offered before rather than after a predictably painful procedure is undertaken. Babies being given a continuous infusion for pain relief should always, therefore, be written up for a further 20 or 40 microgram/kg bolus dose IV not more than once every 4 hours "prn".

If such supplementation does not seem to be bringing relief the situation needs to be reviewed promptly with senior medical staff in the knowledge that, because small babies vary unpredictably in the way in which they 'clear' morphine from their bodies, it is completely inappropriate to rely on a "one dose suits all" regimen when dealing with serous chronic pain. There seems little doubt that severe pain can sometimes require a higher dose than the one recommended in this *Formulary*. Post-operative babies on a ventilator sometimes seem to need boluses of as much as 100 micrograms/kg, or an infusion of 40 micrograms/kg per hour, especially if tolerance has started to develop. Nobody should doubt that babies who are dying are also as deserving of full analgesia as those for whom there is still hope of survival (McHaffie, 2001; Royal College of Paediatrics and Child Health, 2004).

Conclusion: There can be little doubt that ill babies can become stressed; less certainty that they have yet had the experiences necessary to become frightened or anxious. Nothing seems capable of abolishing the acute, but short lasting, pain caused by some intensive care procedures except a general anaesthetic (or local anaesthetic), and few neonatal intensivists have yet acquired any of the basic skills expected of a competent anaesthetist, even if they have no concern for their ability to control the upper airway of an unconscious patient. Ketamine, nitrous oxide, and propofol (q.v.) have been used to obliterate the pain caused by some short term procedures endured by older children, but there is, as yet, very little experience of their use in neonates.

We have learnt from the NEOPAIN trial that it is extremely difficult to judge how much low grade pain and distress babies suffer while receiving respiratory support, and equally difficult to show that any routine continuous infusion of morphine does much to address that discomfort. The dilemma of how to deal with this situation remains unresolved. The only way to deal with *severe* pain is to give an opiate, and morphine still remains by still by far the best studied opiate. We delude ourselves if we think it is easy to judge how much pain a baby is in, or how much relief a morphine infusion has delivered. Babies also vary in the speed with which they clear morphine from the body so much that no single fixed dose regimen is ever going to address this need. To be confident of treating severe sustained pain a high dose infusion is necessary, and that can only be given with safety if breathing is first controlled. That, in turn,

deprives the baby of the ability to cry, and (although we know that pain is far from being the only reason why babies cry) this makes it even harder to judge just how much pain the baby is really in.

In the end we do well to assume [1] that illness causes a baby the same amount of pain and distress as an older child, [2] that it remains important to reduce all painful procedures to a minimum even in a baby receiving high dose morphine analgesia, and [3] that all painful procedures taking more than 1–2 minutes should be done, where possible, under local or general anaesthesia even when the baby is already under opiate sedation. Constant repetition can blunt staff to the pain caused by many 'routines', but parents become increasingly distressed by such repetition, and there can be little doubt that babies do too. Anyone who doubts this only has to read the very vivid letter from a parent on this subject in the correspondence columns of the *Lancet* recently (Bastos, 2003). Several 'consensus' statements have recently given the uncritical reader the impression that we know quite a lot about pain relief and opioid use in the neonate. The more critical overview of the same subject by two nurses (Frank and Miaskowski, 1997) provides a more honest picture of the depth of our continuing ignorance.

Studies comparing different opiate drugs

Morphine v. fentanyl: A study in 1999 concluded that "fentanyl may be superior to morphine for short-term postnatal analgesia in newborn infants" but a careful reading of the text shows that there were actually very few differences between the findings in the two treatment groups. Pain relief was equally satisfactory in both groups, as was the reduction in the plasma adrenaline and noradrenaline levels. Using a high dose regimen for an average of just 2 days (36–107 hours) rather more gastrointestinal stasis was found in those given morphine (38/80) than in those given fentanyl (15/83) when this was judged by the number of meconium stools passed and the amount of fluid aspirated from the indwelling nasogastric tube (the babies were unfed). Urine retention was seen in half the children studied, and equally common in both treatment groups. No significant hypotension was seen in either group, and the start of enteral feeding was not delayed. β-Endorphin levels [measured in a sub-sample of babies] only showed a decrease that was significant in those given fentanyl. While these findings suggest that there may be some advantage in using fentanyl rather than morphine, it is equally possible that the difference seen merely reflects the dose of drug chosen for the study. Neither can it be assumed that the balance of advantage would have still favoured fentanyl if treatment had been continued for more than 2-3 days given the way tolerance to fentanyl changes over time.

Morphine v. diamorphine: Comparative studies of morphine and diamorphine, given as a continuous infusion, have been reported as showing that morphine causes a marginally larger drop in blood pressure. However differences of statistical significance are not necessarily differences of clinical significance, and here is no evidence that the transient early drop in pressure sometimes seen during standard dose treatment is associated with any fall in cardiac output or tissue perfusion. Pain itself can cause a rise in blood pressure. Indeed one standard method of assessing whether neonatal analgesia has been effective is to show that treatment has reduced the body's own production of adrenaline and noradrenaline. A modest fall in blood pressure might be *expected* therefore if the baby was in real pain, and any drop interpreted as showing that treatment was working. It has been argued that the 2 mm Hg drop in mean arterial pressure seen after the start of high dose treatment with morphine shows "that diamorphine is preferable for the sedation of mechanically ventilated preterm neonates" (Wood *et al.,* 1998) but many would not agree with this. The observational study of the haemodynamic effect of morphine published by Sabatino *et al.* in 1997 detected a similar small - but statistically nonsignificant - fall in mean arterial pressure (4%), but was unable to detect any change in cardiac output or in cerebral blood flow velocity. Many reference texts suggest that rapid ***bolus*** administration can cause hypotension, but Rutter and Evans (2000) could find no evidence of this.

Combined use with a benzodiazepine 'anxiolytic'

Benzodiazepines (such as midazolam) are widely used in older children and adults requiring intensive care, and often combined with opioid use. Similar care has become common in some neonatal units but is still only poorly evaluated. While benzodiazepines, on their own, have a sedative effect, they do nothing to combat pain. In the only neonatal controlled trial undertaken to date (the small NOPAIN trial involving 67 babies) the outcome in those given midazolam was worse than in those given morphine or a placebo infusion (Anand *et al.*, 1999), as discussed in the commentary on midazolam. While this could have been a chance finding, it was decided, once these finding became known, not to include midazolam use in the protocol for the larger NEOPAIN trial since morphine provides both sedation and analgesia.

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