Pethidine: to prescribe or not to prescribe? A discussion surrounding pethidine’s place in midwifery practice and New Zealand prescribing legislation

INTRODUCTION

The Midwifery Council of New Zealand (MCNZ) and the New Zealand College of Midwives (NZCOM) are currently working with the Ministry of Health to negotiate changes to the Misuse of Drugs Act (MCNZ, 2013). This will impact on the scope for prescribing within midwifery, and will most likely mean that midwives will be able to prescribe a wider range of controlled drugs for use in intrapartum care. Midwives in New Zealand are legally able to prescribe a Class B controlled drug under the Medicines Act 1981 and Misuse of Drugs Act 1975 and their Amendments and Regulations. Currently, pethidine is the only controlled drug able to be prescribed by midwives but this may be expanded to a choice of three: pethidine, fentanyl and morphine. It is therefore timely to revisit the discussions surrounding the use of pethidine as analgesia in childbirth.

Pethidine is a widespread and current pain management option utilised in New Zealand midwifery practice and is widely available in New Zealand hospitals (Lee & Ho, 2004; Saravanakumar, Garstang & Hasan, 2007). Lee and Ho’s published survey in 2004, investigating the use of obstetric analgesia in New Zealand hospitals, indicated 96% of obstetric facilities in New Zealand used intramuscular pethidine, and 70% used intravenous pethidine (including patient-controlled analgesia) for analgesia (Lee & Ho, 2004). In 2011, pethidine was used by 9.7% of all birthing women using an MMPO member Lead Maternity Carer (LMC) in New Zealand (NZCOM/MMPO, 2012). MMPO, the Midwifery and Maternity Providers Organisation, is a service which provides practice management support to self-employed member midwives including maternity notes and a claiming system that collates and reports on maternity data from birthing women registered with MMPO-member LMCs. Data is collected from the practice information and outcomes generated by its members. Membership is voluntary for self-employed midwives and in 2011 there were 866 member midwives across New Zealand contributing data from 31,739 birthing women, (NZCOM/MMPO, 2012). A total of 32,083 babies were born to these women. The MMPO data therefore represent 51.9% of all registered births in New Zealand in 2011 (NZCOM/MMPO, 2012). Women not included were cared for by non-MMPO LMC midwives or District Health Board (DHB)-employed midwives providing intrapartum care. National data from DHBs are not generally available, but Auckland DHB does produce and make public its statistics in an annual report of data collected from midwives working in their Labour and Birth suite at National Women’s Hospital. The National Women’s Annual Clinical Report trends” (Auckland District Health Board 2012, p.99).

In 2010, a decrease which they commented was “in keeping with international trends” (Auckland District Health Board 2012, p.99).

Changes to the New Zealand Misuse of Drugs Act (1975) regarding the prescription of opioids by midwives are currently under discussion. At this time, pethidine is the only controlled drug able to be prescribed by New Zealand midwives. Pethidine is a synthetic opioid which affects the transmission of pain signals to the central nervous system and induces a state of euphoria and sleepiness. It was first used in midwifery in the United Kingdom to sedate anxious women and was never intended to be prescribed for pain relief. Despite the widespread belief that pethidine is effective at reducing pain and shortening women’s labours, the available evidence does not support this. Significant side effects for both the woman and the baby raise further questions about the suitability and safety of pethidine use in New Zealand maternity care. Relevant New Zealand legislation is currently under review with the potential for changes enabling midwives to offer a wider range of opioids. This article represents sections of a case study submitted as part of the requirements for the third year of study towards a Bachelor of Midwifery at Christchurch Polytechnic Institute of Technology (CPTT). It investigates the use of pethidine as a pharmaceutical method of pain relief in the New Zealand context, and the effects of its administration on the length of a woman’s labour and on neonatal outcomes. Considerations for, and potential changes within, midwifery prescribing practices are then discussed.

ABSTRACT

Changes to the New Zealand Misuse of Drugs Act (1975) regarding the prescription of opioids by midwives are currently under discussion. At this time, pethidine is the only controlled drug able to be prescribed by New Zealand midwives. Pethidine is a synthetic opioid which affects the transmission of pain signals to the central nervous system and induces a state of euphoria and sleepiness. It was first used in midwifery in the United Kingdom to sedate anxious women and was never intended to be prescribed for pain relief. Despite the widespread belief that pethidine is effective at reducing pain and shortening women’s labours, the available evidence does not support this. Significant side effects for both the woman and the baby raise further questions about the suitability and safety of pethidine use in New Zealand maternity care. Relevant New Zealand legislation is currently under review with the potential for changes enabling midwives to offer a wider range of opioids. This article represents sections of a case study submitted as part of the requirements for the third year of study towards a Bachelor of Midwifery at Christchurch Polytechnic Institute of Technology (CPTT). It investigates the use of pethidine as a pharmaceutical method of pain relief in the New Zealand context, and the effects of its administration on the length of a woman’s labour and on neonatal outcomes. Considerations for, and potential changes within, midwifery prescribing practices are then discussed.

KEY WORDS

Pethidine, analgesia, opioids, prescribing, midwives, New Zealand legislation
and cost rather than through robust consideration of evidence and alternatives. Tuckey, Prout and Wee (2008) found that the majority of consultant and midwife-led units in the UK (84.4%) used pethidine over diamorphine or morphine due to tradition and familiarity rather than drug efficacy. Panda, Desbiens, Doshi and Sheldon (2004) found that the low cost of pethidine also influenced its choice.

This article represents sections of a case study submitted as part of the requirements for the third year of study towards a Bachelor of Midwifery at the Christchurch Polytechnic Institute of Technology. It investigates the use of pethidine as a pharmaceutical method of pain relief and the effects of its administration on the length of a woman’s labour, neonatal outcomes, and the woman’s experience. Implications and considerations for midwifery practice, potential changes to prescribing legislation, and areas for further research are highlighted.

**PHarmacology of Opioid Drugs**

Opiates are naturally-occurring substances derived from the opium poppy which bind to opioid receptors in the central nervous system (the brain and spinal cord). A range of opioid substances exist which have the same pharmacological action as natural opiates. Pethidine is one such synthetic opioid. All opioid drugs affect transmission of pain to the central nervous system so that perception of, and emotional response to, pain is diminished and a state of euphoria and sleepiness/sedation is induced (Mander, 2011; Yerby, 2000).

Each opioid comes with its own selection of side effects dependent on its action on central nervous system receptors. When the caregiver is considering opioids for pain relief in labour, the optimal choice will have rapid onset of effect, be efficiently metabolised and eliminated, and have minimal side effects (Anderson, 2011). Pethidine, morphine and fentanyl work primarily on mu receptors, which are responsible for mediating sedation, analgesia, nausea, vomiting, pruritis, euphoria, respiratory depression, and urine retention (Anderson, 2011). These bodily responses will therefore be enhanced when the drug is used, producing unwanted side effects. Of the three drugs being considered, pethidine is the weaker agonist and thus the less potent analgesic. Furthermore, pethidine produces an active metabolite, norpethidine, which has a very long half-life. Norpethidine and its effects on the baby will be discussed later in this article. A comparison of half-lives can be seen in Table 1.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Usual Dose</th>
<th>Half-Life</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pethidine</td>
<td>100 mg</td>
<td>Pethidine</td>
</tr>
<tr>
<td></td>
<td>Maternal 3-7 hours</td>
<td>Neonatal 18-23 hours</td>
</tr>
<tr>
<td></td>
<td>Adults 21 hours</td>
<td>Neonatal 63 hours</td>
</tr>
<tr>
<td></td>
<td>*Metabolites</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Adults 2-4 hours</td>
<td>Neonatal 13.9 hours</td>
</tr>
<tr>
<td>Morphine</td>
<td>10 mg</td>
<td>Morphine</td>
</tr>
<tr>
<td></td>
<td>Maternal 43 minutes</td>
<td>Neonatal 6.5 hours</td>
</tr>
<tr>
<td></td>
<td>Adults 2-4 hours</td>
<td>Neonatal 13.9 hours</td>
</tr>
<tr>
<td></td>
<td>*Metabolites</td>
<td></td>
</tr>
<tr>
<td>Fentanyl</td>
<td>100 mcg intermittent bolus</td>
<td>Fentanyl</td>
</tr>
<tr>
<td></td>
<td>intravenous doses</td>
<td>Adults 3-4 hours</td>
</tr>
<tr>
<td></td>
<td>Neonatal 1-7 hours</td>
<td>No active *metabolites</td>
</tr>
</tbody>
</table>

*Metabolites are small molecules produced during metabolism which remain in the body after a drug is broken down. Profiling metabolites is an important part of drug discovery, leading to an understanding of any undesirable side effects (Kumar, Abbas, Fausto & Aster, 2009; Anderson, 2011).

**History of Use in Midwifery**

The ability to achieve sedation and pain relief through chewing or ingesting opium poppy seeds has been known for about 25 centuries. The actual extract of morphine from the opium poppy was first discovered in 1805. The name, morphine, was coined by a German pharmacist, Adolf Sertturner (1905), who took it from Morpheus, the mythological god of dreams. Morphine extract enabled a specific, measured dose to be swallowed as a liquid. It was not until the syringe and needle were invented in Edinburgh, Scotland, in 1853 that morphine could be given via injection. Morphine was first used for women in labour in the early 1900s. It was initially mixed with other sedatives and injected into the woman’s vein to induce what was called ‘twilight sleep’. These drugs usually made the woman semiconscious (or totally unconscious), often leaving her with no memory of the actual birth (Leavitt, 1980; Sandelowski, 1984).

Pethidine itself was first used in Germany in 1939 as sedation and pain relief for wounded troops during the Second World War (Squire, 2000). It spread rapidly throughout society and was widely celebrated by women suffering dysmenorrhoea, so much so that by the late 1940s many were addicted. Its use became regulated in 1949, around the time midwives began using it for labour (Squire, 2000). In midwifery, pethidine was referred to as “sedation” and was used to reduce anxiety in labour (Bamfield, 1997). This practice of using such sedative type drugs to “induce sleep… and relax rigidity of the soft parts” and therefore improve slow progress in childbirth has been used across the history of labour care (Fairbairn, 1918, cited in Bamfield, 1997, n.p.). Yet, pethidine is now generally regarded as an analgesic despite its lack of pain-relieving ability. Historically it is suggested that it was only ever used to help relax/sedate a woman, thus reducing her “rigidity” and speeding her labour progress. The poor analgesic effectiveness of pethidine is the topic of much discussion. Therefore, examining the effectiveness of pethidine for reducing length of labour, and women’s experience of its relaxing/sedating effect, appears more appropriate than critiquing its actual analgesic efficacy.

**Pethidine Use to Shorten Labour**

The evidence surrounding the effect of pethidine on length of labour is scant. Pethidine did not undergo randomised controlled trials (RCTs) prior to its introduction into clinical practice; instead its results were documented through case studies (Shipton, 2006). Most studies were single-arm trials carried out between the 1940s and 1960s which makes the quality and relevance of their results questionable. Some authors concluded from these studies that pethidine shortened labour, others claimed it lengthened labour, and still others decided it did both, depending on which stage of labour it was given (Thomson & Hillier, 1994; Crafter, 2000; Hill & McMackin, 2012). A letter to the editor of the British Medical Journal in July 1947 conveys the most commonly held theory that had emerged by this time - that pethidine relaxed women enabling labour to progress. The author claimed that in cases of “rigid cervix”, women were so completely relaxed by pethidine that labour was shortened “dramatically” (Waters, 1947, p. 71).

Thomson and Hillier (1994) state that it has long been recognised within midwifery in the UK that pethidine relaxes women and that their labours then progress rapidly. They were surprised when a pilot randomised controlled trial comparing pushing methods inadvertently highlighted longer labours for the women who given pethidine. The difference was statistically significant (p=0.01, 95% CI). Following this discovery, an attempt by Thomson and Hillier (1994) to carry out a review of trials investigating pethidine and length of labour failed to find sufficient evidence due to a lack of RCTs. The authors were forced to conclude that pethidine’s effect on labour length had not been adequately studied and no conclusions could be drawn.

In 2004 a randomised controlled trial of 407 women was conducted in Uruguay where pethidine is frequently used to treat dystocia in the first stage of labour (Sosa et al. 2004). This is the only available high qualityRCT focusing on length of labour and the authors found no significant difference in the total length of labour between women receiving pethidine...
and those receiving a placebo. There was an increase in adverse effects for women receiving pethidine, especially dizziness (relative risk 4.68, 95% CI) and the need for oxytocin augmentation; there was also a higher incidence of Apgar scores <7 at 1 minute of age (relative risk 4.11, 95% CI) (Sosa et al, 2004). A small RCT with 150 labouring women in Iran found similar results, with no significant difference in length of labour for women receiving either pethidine or a placebo (Sehkvat & Behdad, 2009). Mansoori, Adams and Cheater (2000) found that women in their cohort study receiving pethidine had longer labours compared to women with no pain relief; but shorter labours than those with epidural anaesthesia (p<0.001, 95% CI). From reviewing the available literature there is no evidence to support pethidine as a method of shortening labour despite the apparent widespread belief dating from the 1940s of its ability to do this.

SEDATION AND THE WOMAN’S EXPERIENCE

A recent Cochrane systematic review of opioids in labour found that they all provide poor pain relief (Ullman, Smith, Burns, More & Dowswell, 2011). Opioids all caused significant side effects including drowsiness and nausea. However, the authors state that the studies available were of poor quality, with largely insignificant results and their review failed to provide sufficient evidence for or against pethidine compared with other opioids.

Many of the available studies compare pethidine to other opiates to investigate effectiveness of pain relief, the appropriateness of which was questioned earlier. For example, Fairlie, Marshall, Walker and Elbourne (1999) found that diamorphine was moderately superior at relieving pain and resulted in less vomiting than pethidine. A frequently quoted study by Olofsson, Ekblom, Ekman-Ordeberg, Hjeml, and Irestedt (1996) highlighted the ineffectiveness of all opioid drugs on labour pain, and found no significant change in pain scores following pethidine or morphine administration. In their study, 75% of women went on to request an epidural, and significantly more women receiving pethidine experienced nausea and vomiting than those receiving morphine (p=0.03, 95% CI). However, pethidine was more effective at calming women (p<0.03, 95% CI) although both drugs caused significant maternal sedation (Olofsson et al, 1996). As the authors state, these results support pethidine's ability to dull emotional reaction to pain (sedate), rather than to provide ‘true analgesia’. This is also supported by Kranke et al. (2013) who describe both pethidine and morphine as causing heavy sedation. A recent study by Madden, Turnbull, Cyna, Adelson and Wilkinson (2013) surveyed 123 women about their experiences of a range of physical, psychosocial and pharmacological methods of pain relief and found that pethidine was the least preferred of all methods.

New Zealand women have the benefit of continuity of midwifery care and the opportunity to discuss pain relief options in depth with a known caseloading community-based midwife throughout their antenatal period. Comments from New Zealand women on online fora appear to show an understanding of the way pethidine works and an acceptance of its use as a sedative rather than a pain killer, although not all women enjoyed the sensations:

- It made me so relaxed and distanced myself from the pain (anonymous contributor to OHbaby!, 2012).
- I found pethidine took the edge out of the contractions and that helped me relax and allow the cervix to do its job without me fighting it coz of the pain it was causing, which in result did help speed up the dilating [sic] of cervix (anonymous contributor to Treasures, 2010).
- I had pethidine - it made me feel really out of it and I felt like I was not in control (anonymous contributor to Treasures, 2010).

Feeling out of control as an effect of pethidine has been highlighted by Jantjes, Strumphe, & Kotze (2007). The authors reported dizziness, confusion, and sleepiness, and stressed the importance of midwives informing women of these expected effects. The ethics of offering a woman a drug known to have little analgesic effect but significant sedative effects, which could impact her ability to make decisions or even remember her labour, must be considered.

From reviewing the available literature there is no evidence to support pethidine as a method of shortening labour despite the apparent widespread belief dating from the 1940s of its ability to do this.

SIGNIFICANT FETAL AND NEONATAL CONCERNS

Pethidine readily crosses the placenta with maximum levels found in the baby's bloodstream between one and five hours following maternal administration (Tuckey, Prout & Wee, 2007). Fetal effects include reduced short term beat-to-beat variability of the fetal heart and neonatal effects include reduced Apgar scores, depressed muscle tone, respiratory effort, and sucking ability (Reynolds, 2010; Hill & McMackin, 2012). Other studies have raised additional concerns regarding the potential association between use of opioids in labour and development of neonatal drug dependency in later life, though this has not been proven (Nyberg, Allebeck, Eklund & Jacobson, 1993; El-Wahab & Robinson, 2011; Jacobson et al, 1990; Nyberg et al, 2000).

A randomised controlled trial by Sosa et al (2006) found decreased umbilical cord pH between four and six hours after maternal administration, with the lowest level at 4.94 hours. In a recent literature review, Reynolds (2011) stated that acidosis and respiratory depression in babies are maximised if pethidine is given three to five hours before birth but are barely discernible if given within an hour of birth since the drug has not reached sufficient levels in the baby. This is in contrast to the widely-held belief that pethidine’s effects are most detrimental to babies when given close to the birth (personal communication and anecdotal evidence, 2010-2012). Regardless of their effects on respiratory depression, the longer lasting influence of pethidine's metabolites will persist regardless of timing of dose. These effects may be more subtle or 'hidden' at birth, but will go on to affect the baby for several days while the original dose of pethidine is being metabolised by the baby’s liver.

Pethidine is metabolised to norpethidine, a toxic substance which can increase serotonin levels in the central nervous system and is a potent convulsant. It has a half-life of 14 to 21 hours in adults (Shipton, 2006). This half-life is much longer than that of morphine and its metabolite, or fentanyl (see Table 1). The accumulation of norpethidine in babies is potentially more dangerous owing to babies’ reduced elimination abilities and norpethidine’s extremely long half-life of 63 hours (Calvert, Hunter & Eddy, 2012; Anderson, 2011). An opiate antagonist, naloxone, is available to treat babies experiencing respiratory depression but its effects wear off before those of pethidine due to naloxone's relatively short half-life. Naloxone is not effective against norpethidine itself. A review of naloxone failed to find enough evidence of clinical benefits for its use as part of resuscitation of babies born to mothers who had received pethidine and recommended further research in the form of randomised controlled trials (Fowlie & McGuire, 2003). Herschel, Khoshnood and Lass's study
The profession is aware of the need for change in the availability of, and education surrounding, all opioids within midwifery.

PRESCRIBING LEGISLATION UNDER REVIEW

From the above critical review, it is difficult to recommend the use of pethidine as an effective and safe analgesic for use during labour. However, in the current absence of more suitable options it continues to be the most widely available pharmaceutical in midwifery excepting Entonox
Legislation is under review and it is anticipated that in time New Zealand law may be changed to enable midwives to prescribe morphine and fentanyl as well as pethidine.

(a gas consisting of 50% nitrous oxide and 50% oxygen), and is the only controlled drug able to be prescribed by New Zealand midwives. The MCNZ considers the prescription of opioid drugs to be within the midwifery scope of practice (MCNZ, 2011); midwives are legally able to prescribe a Class B controlled drug under the Medicines Act 1981 and Misuse of Drugs Act 1975 and their Amendments and Regulations. The NZCOM expects midwives to be competent to prescribe pethidine within their scope of practice (NZCOM, 1995).

It has already been suggested that the legislation restricting the prescription of controlled drugs to pethidine only is removed, and a gazetted list of controlled drugs is implemented instead. On the 5th of April 2011 the MCNZ and NZCOM filed a submission to the Health Select Committee supporting the intent of the upcoming Medicines Amendment Bill to review and amend the Misuse of Drugs Act. This is still a work in progress (MCNZ, 2013). The current legislation may be directed by tradition rather than evidence (Tuckey, Prout & Wee, 2008). This legislation is perhaps out of date, since recent evidence suggests that other opioids, namely morphine or fentanyl, may be safer for babies and cause fewer adverse effects than pethidine (MCNZ, 2011). The New Zealand College of Midwives supports this view (NZCOM, 2012). Expanding our legislation would provide an excellent opportunity for women who choose an LMC midwife to discuss and formulate individual plans for pain management in labour. The New Zealand partnership model provides an excellent opportunity for women who choose an LMC midwife to discuss and formulate individual plans for pain management in labour. At this time, pethidine is the only controlled drug New Zealand midwives may prescribe. Legislation is under review and it is anticipated that in time New Zealand law may be changed to enable midwives to prescribe morphine and fentanyl as well as pethidine. This will open the door for richer discussion and wider choice for midwives and women.

CONCLUSION

Pethidine offers temporary, relatively weak analgesia. It is an effective sedative, inducing sleepiness, and reduced awareness and control. It has long been believed that pethidine shortens labour but the current available evidence suggests this is not the case. Ideally, opioids chosen for midwifery use will have rapid onset of effect, be efficiently metabolised and eliminated, and have minimal side effects. Pethidine causes more side effects than other opioids such as morphine and fentanyl; these other drugs have shorter half-lives and may also have fewer undesirable effects on newborns. Further research into the use of naloxone in resuscitation, and opioid effects on breastfeeding and newborn behaviour, is essential while opioids continue to be used for childbirth.

Antenatal and intrapartum discussion and support are key aspects of midwifery practice which should address the evidence and women's wishes surrounding pain management. The New Zealand partnership model provides an excellent opportunity for women who choose an LMC midwife to discuss and formulate individual plans for pain management in labour. In this way, pethidine is the only controlled drug New Zealand midwives may prescribe. Legislation is under review and it is anticipated that in time New Zealand law may be changed to enable midwives to prescribe morphine and fentanyl as well as pethidine. This will open the door for richer discussion and wider choice for midwives and women.

REFERENCES


