Breastfeeding after anaesthesia: a review of the pharmacological impact on children

T. C. CHU*, J. McCALLUM†, M. F. YII‡
Department of Anaesthesia, Wyong Hospital, Wyong, New South Wales, Australia

SUMMARY
Post-anaesthetic advice imparted to breastfeeding mothers can vary. This is due in part to the differing information from published data, product information sheets and inevitably from the unhindered flow of opinions available on the internet. This literature review examined the evidence relating to drugs commonly used in the modern anaesthetic setting and their impact on breastfed children. It suggests that special precautions are rarely warranted in the post-anaesthetic care of breastfeeding patients.

Key Words: anaesthesia, breastfeeding, breastmilk transfer, neonates, infants

In the field of obstetric anaesthesia, the placental transfer of drugs is a shared and incontrovertible focus for both anaesthetic and neonatal clinicians. However, opinions about anaesthetic drug transfer via breastmilk are far from uniform. Data on the transfer of anaesthetic and analgesic drugs into breastmilk are somewhat limited due to the difficulties in recruiting nursing mothers and neonates for controlled studies. Consequently, advice on matters such as milk discards, feed delays or whether precautions are needed can vary depending on which hospital or medically-endorsed guideline is sought. In addition, objective evidence relevant to this subject may be cumbersome for clinicians to sift through and practically impossible for the public to clearly decipher. Much of the information published by pharmaceutical companies consists of generic warnings, with wording more akin to legal disclaimers than authoritative medical advice. For these reasons we have compiled a tabulated summary of the current evidence for drugs used in anaesthetic practice and their impact on children via breastmilk.

METHODS
Anaesthetic drugs and commonly used adjuvants were identified from our departmental formulary and sub-classified into the standard categories of inhalational anaesthetics; premedication and induction drugs; neuromuscular blocking and reversal drugs; opioids; local anaesthetics; non-opioid analgesics; anticoagulants; anti-emetics; antibiotics; and other. Advanced resuscitative drugs (e.g. adrenaline or dantrolene) were not considered due to the non-elective nature of their use.

A literature search was conducted for each of the drugs stocked for perioperative use at our hospital (48 in total) using the Medline, PubMed and Embase databases as search tools. Keywords such as ‘anaesthesia’, ‘breastfeeding mothers’, ‘breastmilk transfer’ and ‘neonates’ were used. The bulk of data retrieved originated from case reports or series (Level 4 evidence based on levels of evidence used by the Centre for Evidence Based Medicine¹) for example articles by Stuttman et al⁰ on remifentanil and xenon, and Madadi et al⁰ on codeine. The search did not identify any systematic reviews of cohort studies (Level 2a) and only a handful of articles of Level 2 evidence, since studies involving breastfeeding mothers and neonates were scarce. Notable studies include limited controlled trials by Wilson et al⁰ (Level 2b) and Beilin et al⁰ (Level 2b) on epidural fentanyl and a retrospective cohort study by Lam et al⁰ (Level 2b) on oxycodone. Review articles drew conclusions from clinical data cited from earlier publications.

Fifty-two of the 54 references identified (96%) were published in the period from 1990–2012. With respect to the context of breastfeeding, a small number of well-established drugs had not appeared in the published literature for several decades. The two older articles referred to neostigmine (Fraser and Turner¹, 1963) and metronidazole (Passmore et al⁰, 1988).
Commercial formularies, such as the Monthly Index of Medical Specialties, were also consulted to locate referenced articles but were not used as primary sources of data. The findings were then tabulated according to the classes of action and the relative safety of each drug.

RESULTS

Current evidence suggests that breastfeeding need not be interrupted nor modified following a standard anaesthetic. General measures are recommended to minimise the impact of surgery and anaesthesia on lactation and feeding patterns. These general measures include: feeding as close to the pre-anaesthetic period as possible; expressing and storing breastmilk for later use when the mother is in surgery and recovery; and adequate hydration (especially intravenous hydration during the fasting period and providing an additional 500–1000 ml for fluid loss associated with breastfeeding).

All drugs commonly used in the anaesthetic setting have long been used on lactating patients. Reports of serious reactions are rare and contraindications are relative in otherwise healthy mothers and term babies. Awareness of the following findings will help minimise adverse outcomes.

Drugs with no milk transfer or safety verified by targeted studies

The scope of drugs available for modern general and regional anaesthesia is wide enough that direct adverse impact on the nursing mother or infant can be avoided. By virtue of their chemistry (e.g. large, polarised neuromuscular blocker or local anaesthetic molecules) or their pharmacokinetics (e.g. rapid elimination of volatile anaesthetics), many of the commonly used drugs do not cross into lactating ducts in any meaningful quantities, if at all. This is certainly true for warfarin, a drug required by some obstetric patients, because its polarity and its 99% bond to albumin render it undetectable in breastmilk. When specifically tested in breastfed infants, no alteration was demonstrated on their coagulation profiles.

Metoclopramide has been used to promote lactation in breastfeeding mothers and no adverse impact on infants has been reported. Xenon and neostigmine are undetectable in human breastmilk after their administration to lactating mothers. Heparin does not cross into breastmilk as well, while glycopyrrolate, nitrous oxide and isoflurane have negligible transfer. Thiopentone, propofol, midazolam, enoxaparin, lignocaine, bupivacaine, ropivacaine, fentanyl, tramadol and paracetamol are all excreted in human breastmilk in doses that are too low to be clinically significant.

Although high-dose labour epidural fentanyl (>150 μg) was found to be associated with a higher incidence of bottle feeding at six weeks postpartum, there was no detectable effect on initiation of breastfeeding or on neonatal respiration. Conversely, adjuvant epidural fentanyl has been demonstrated to improve patient satisfaction, reduce local anaesthetic usage and consequent motor blockade. Further studies are required before concluding whether or not epidural fentanyl has lasting ill-effects on neonates. Similarly, the safety of epidural pethidine in the patient-controlled epidural analgesia mode was also verified when the levels of both pethidine and norpethidine were consistently subclinical in targeted measurements.

For drugs that are known to be detectable in breastmilk, many were still found to be safe for the nursing infant. These include metronidazole, ampicillin and gentamicin, all of which have been classified by the American Academy of Pediatrics as compatible with breastfeeding.

In the case of nonsteroidal anti-inflammatory drugs, only aspirin recorded an adverse impact on nursing infants. All other nonsteroidal anti-inflammatory drugs were detected in human breastmilk in concentrations that were too low to affect neonates. Likewise, single doses of parecoxib (and hence valdecoxib) were detectable in breastmilk after caesarean deliveries without a demonstrable effect on neonates.

The amount of nicotine passed into human breastmilk via a transdermal patch varies according to the patch’s strength, but manifests in concentrations lower than those from smoking. The use of nicotine patches does not affect the milk intake of breastfed infants.

Drugs known to have potential or mild impact in infants

Droperidol has been used to prevent and treat maternal nausea and vomiting associated with morphine patient-controlled analgesia after caesarean delivery, and a decrease in neurological status in the breastfed infants has been observed. The clinical significance of this has not been elucidated.

Caffeine, sometimes prescribed for lactating mothers who suffer from post-dural puncture headache, has been shown to have little to no effect on the breastfed infant after occasional use. Nevertheless, it would seem advisable to restrict caffeine consumption to less than 300 mg/day due to the risk of depleting the iron content of breastmilk. There are also reports of irritability in breastfed infants after maternal consumption of high doses.

Morphine, pethidine and methadone are all known to be excreted in human breastmilk. No studies to date have shown an adverse impact on the

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breastfed infant of mothers receiving methadone, low or single doses of morphine and epidural or single doses of pethidine. Larger and repeated maternal doses of intravenous pethidine, however, did produce signs of neurobehavioural depression in breastfed neonates. Amongst the pethidine cohort, neonates of mothers using comparable doses of patient-controlled intravenous pethidine (4.7 mg/kg) or morphine (0.54 mg/kg) in the first 48 hours postpartum demonstrated lower levels of alertness and orientation on day three of life. For women with chronic opioid use throughout pregnancy, particularly methadone, breastfeeding is recommended, but gradual weaning is warranted to avoid neonatal opioid withdrawal.

Drugs known to have caused serious adverse effects in infants

Although short-term use of diazepam was thought to be compatible with breastfeeding, diazepam has also been demonstrated to cause sedation and feeding difficulties in some breastfed infants. In the modern era, abundant alternatives are available as substitutes for diazepam. Likewise in the case of aspirin, where a case of infantile metabolic acidosis has been described, a myriad of alternative nonsteroidal anti-inflammatory drugs that safely meet the pharmacological needs of the mother are available.

The variability of maternal metabolism of codeine to morphine, in combination with the neonate's immature metabolism, was implicated in the death of one breastfed infant whose mother was prescribed codeine. High levels of morphine were detected in this infant, due to maternal ultra-rapid metabolism of codeine to morphine. The frequency of this CYP2D6 genotype for 'ultra-rapid' metabolism is 1-7% amongst Caucasians, just a little less than the 10% of Caucasians who possess the 'slow' metabolising genotype. Although doubts have been cast on the accuracy of this initial claim, further studies have revealed central nervous system depression in breastfed neonates as a result of codeine administration to the mother. These effects have only been detected in the infant after four days of maternal codeine administration.

Oxycodone shares the same cytochrome pathway of metabolism, and oxymorphone is one of its active metabolites. Conflicting evidence exists about the safety profile of oxycodone in nursing infants. One study supported the long safety record of oxycodone for post-caesarean analgesia after measuring the milk and plasma concentrations of mothers and neonates. This study concluded that the amount ingested by a newborn is negligible. Conversely, a recent retrospective survey revealed a level of neonatal sedation comparable to that seen when mothers use codeine.

No human data

There is a group of drugs for which studies to detect presence in breastmilk have not been conducted. These generally fall into one of two categories: those that are well-established in practice following years of use (e.g. succinylcholine, atropine, ketamine, sevoflurane, desflurane, remifentanil, alfentanil, ondansetron, prochlorperazine, vancomycin and cephalothin) or drugs relatively new to the market (e.g. dexametomidine, sugammadex). A minor exception to this categorisation is dexamethasone. Although specific human data are absent, an extensive history of other corticosteroids being used maternally in the perinatal period has yielded no evidence of neonatal effects via breastmilk.

For these drugs, there are only original product information pamphlets stating that human data is not available. Clinical use, despite the absence of data, may be justified for older drugs based on the absence of adverse case reports among breastfed infants, especially if the drug is also approved for paediatric use.

CONCLUSION

The conclusions drawn are limited by the scarcity of large or robust studies evaluating the transfer of a number of perioperative drugs into breastmilk. Adequate recruitment of subjects is challenging due to the scarcity of breastfeeding women in need of surgical and anaesthetic services beyond the perinatal period. Furthermore, consent for phase II drug trials is unappealing to new mothers, especially if invasive tests on their newborns are required. Nevertheless, current evidence suggests that once the postoperative mother is alert and comfortable to do so, breastfeeding can and should resume with minimal interruption. Commonsense measures are recommended to minimise the impact an anaesthetic has on breastfeeding. A standard, one-off exposure to general and/or regional anaesthetic drugs should not be viewed as an impediment to breastfeeding. Conversely, the judicious use of adequate analgesia for postoperative mothers should not be compromised for the sake of breastfeeding. Drugs such as diazepam and codeine should be avoided if possible. A case also exists to extend breastfeeding studies and measurements for children beyond the neonatal age, where an increased amount of milk consumption, and hence the overall drug ingestion, may show a different pharmacodynamic profile. A summary of the safety profiles of the drugs evaluated in this study is provided in Table 1.
### Table 1
Categorised summary of drug safety associated with breastfeeding in the perioperative setting

<table>
<thead>
<tr>
<th>Proven to be safe (nil to negligible trace in breastmilk)</th>
<th>Detectable in breastmilk but no known adverse effects</th>
<th>Potential or mild impact</th>
<th>Serious adverse reactions</th>
<th>No human data available but no reports of adverse effects on breastfed infants</th>
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<tr>
<td><strong>Inhalational anaesthetics</strong></td>
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<tr>
<td>Isoflurane(^{32})</td>
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<td>Sevoflurane(^{36,42})</td>
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<td>Nitrous oxide(^{48})</td>
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<td></td>
<td>Desflurane(^{59})</td>
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<td>Xenon(^{2})</td>
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<td><strong>Premedicant and induction drugs</strong></td>
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<tr>
<td>Thiopentone(^{42})</td>
<td></td>
<td></td>
<td></td>
<td>Diazepam(^{36,42}) (esp. chronic use)</td>
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<tr>
<td>Propofol(^{13,19})</td>
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<td>Dexamethomidine</td>
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<td>Midazolam(^{19})</td>
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<td>Ketamine</td>
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<td><strong>Neuromuscular blocking and reversal drugs</strong></td>
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<tr>
<td>Neostigmine(^{7})</td>
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<td>Succinylcholine</td>
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<td>Glycopyrrolate(^{46})</td>
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<td>Atropine(^{50})</td>
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<tr>
<td>Non-depolarisers(^{2}) (quaternary ions unlikely to cross into milk ducts)</td>
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<td>Sugammadex</td>
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<td><strong>Opioids</strong></td>
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<tr>
<td>Fentanyl(^{14,12,42}) (parenteral and epidural)</td>
<td>Remifentanil(^{2}) (in conjunction with xenon)</td>
<td>Pethidine (intravenous, multi-dose)(^{48})</td>
<td>Codeine(^{55-57}) (use &gt;4 days)</td>
<td>Alfentanil(^{55})</td>
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<tr>
<td>Tramadol(^{13})</td>
<td>Morphine(^{12,42})</td>
<td>Oxycodeone(^{54,6}) (esp. older children)</td>
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<tr>
<td></td>
<td>Methadone(^{26}) (caution with abrupt withdrawal)(^{44})</td>
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<td></td>
<td>Pethidine (single dose)(^{12,26})</td>
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<td></td>
<td>Pethidine (epidural)(^{26})</td>
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<td><strong>Local anaesthetic agents</strong></td>
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<td>Lignocaine(^{11})</td>
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<td>Bupivacaine(^{51,22})</td>
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<td>Ropivacaine(^{9})</td>
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<td><strong>Other analgesics</strong></td>
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<td>Paracetamol(^{12,4})</td>
<td>Parecoxib(^{23})</td>
<td>Aspirin(^{18})</td>
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<td>NSAIDs(^{6})</td>
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<td><strong>Anticoagulants</strong></td>
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<td>Heparin(^{7})</td>
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<td>Enoxaparin(^{8})</td>
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<td>Warfarin(^{11})</td>
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<td><strong>Anti-emetics</strong></td>
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<tr>
<td>Metoclopramide(^{14,46})</td>
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<td>Droperidol(^{15})</td>
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<td>Ondansetron</td>
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<td>Prochlorperazine</td>
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<td></td>
<td></td>
<td>Dexamethasone(^{53})</td>
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