Pediatric Anesthesia

Pediatric Anesthesia ISSN 1155-5645

REVIEW ARTICLE

Safety of the breast-feeding infant after maternal anesthesia

Priti G. Dalal[1], Jodi Bosak[2] & Cheston Berlin[3]

1 Department of Anesthesiology, Penn State University College of Medicine, Milton S Hershey Medical Center, Hershey, PA, USA
2 Anesthesiologists of Greater Orlando, Winter Park, FL, USA
3 Department of Pediatrics, Penn State University College of Medicine, Milton S Hershey Medical Center, Hershey, PA, USA

Keywords
breast-feeding; anesthesia; infant

Correspondence
Priti G. Dalal, Department of Anesthesiology, Penn State Hershey Medical Center, 500 University Drive, H187, Hershey, PA 17033, USA
Email: pdalal@hmc.psu.edu

Section Editor: Adrian Bosenberg

Accepted 20 November 2013

doi:10.1111/pan.12331

Summary

There has been an increase in breast-feeding supported by the recommendations of the American Academy of Pediatrics and the World Health Organization. An anesthesiologist may be presented with a well-motivated breast-feeding mother who wishes to breast-feed her infant in the perioperative period. Administration of anesthesia entails acute administration of drugs with potential for sedation and respiratory effects on the nursing infant. The short-term use of these drugs minimizes the possibility of these effects. The aim should be to minimize the use of narcotics and benzodiazepines, use shorter acting agents, use regional anesthesia where possible and avoid agents with active metabolites. Frequent clinical assessments of the nursing infant are important. Available literature does suggest that although the currently available anesthetic and analgesic drugs are transferred in the breast milk, the amounts transferred are almost always clinically insignificant and pose little or no risk to the nursing infant.

Introduction

Human milk is the ideal source of nutrition in neonates and infants (1–4). It is been the recommendation of both the World Health Organization (WHO) and the American Academy of Pediatrics (AAP) that infants be exclusively breast-fed up to 6 months of age and continue to receive only human milk as the source of milk until 1 year of age (1,4). As a result, there has been an upward trend toward the practice of breast-feeding. In fact, up to 90% of women worldwide, breast-feed their infants (5). There are several advantages of breast-feeding for the baby–maternal and infant bonding, development of immunity of the neonate/infant, and optimal nutrition to the baby (1,6–9). Advantages for the mother include–postpartum involution of the uterine size, reduced risk of ovarian and breast cancer, protection from developing type 2 diabetes, and contraception during the period of exclusive breast-feeding (6,7,10,11).

Concerns may be raised that because the anesthetic agents and perioperative medications are secreted in breast milk, these may have harmful effects on the baby. The decision to permit breast-feeding after maternal treatment with any drug must balance safety and benefit to the infant. An important question is how long a mother should wait after receiving anesthesia and/or analgesia before the baby can be safely breast-fed. Few studies have addressed this issue (12–15). The surgeon, pediatrician and anesthesiologist may be faced with the management of the baby and its nursing mother who needs anesthesia and/or analgesia postpartum or for a surgical procedure. Concerns that may arise include: safety of general anesthesia and perioperative medication use, postoperative analgesia, pumping and discarding the breast milk, impact on breast milk production, extent of monitoring of the infant and special circumstances involving the infant, for example, prematurity, twin baby, and the presence of neonatal clinical situations including congenital syndromes. With the increase in breast-feeding of infants, a review regarding anesthesia and breast-feeding, the transfer of anesthetic drugs into the human breast milk and their effects on the infant would be useful, especially with the use of newer agents. The aim of this article is to review the currently available literature regarding safety of anesthesia and

© 2013 John Wiley & Sons Ltd

related drugs in lactating women and their potential effects on the breast-fed infant.

Physiology and Pharmacology of breast milk

Human milk is secreted by alveolar tissue in the breast and is regulated by prolactin and oxytocin, hormones that are secreted by the anterior and posterior lobes of the pituitary gland, respectively (16). During pregnancy, there is an increase in the level of prolactin, estrogens, and progesterone, which cause the lobuloalveolar development of the breast. Following placental delivery, there is a sudden decline in the levels of estrogen and progesterone, which initiates lactation. Suckling by the baby evokes reflex release of oxytocin and ejection of milk. Suckling also stimulates release of prolactin, which maintains and augments milk secretion. Following the birth of the baby when the mother starts breast-feeding, the early milk secreted for the first 48–72 h is high in protein (rich in antibodies) and low in fat and is called 'colostrum'. Once normal milk secretion is established, upon initiation of breast-feeding, the infant receives initial watery milk called 'foremilk' followed by thicker high lipid content milk called the 'hind milk'. The ability or inability to breast-feed the infant or extract milk by pumping of the breast depends on several factors that include: the ability of the baby to suck, occurrence of illness in either mother or infant, maternal stress, dehydration, use of medications, and the timing and frequency of nursing or pumping of the breast milk (4). The stress of anesthesia, surgery, and the associated illness may influence the mother's ability to produce milk. Additionally, oral contraceptives used in the postpartum period, especially those containing estrogen, may decrease milk supply. Substances called galactogogues to increase milk production include herbal preparations as well as domperidone and metoclopramide (17,18). However, controlled studies to demonstrate both safety and efficacy of these compounds are lacking. In the United States, herbal preparations are excluded from regulation by the United States Food and Drug Administration (FDA) unless a significant safety issue arises. Thus, they are not recommended for use by either the pregnant or the nursing mother. When the mother is not able to breast-feed the baby, maternal milk can be pumped manually or with a breast pump. The pumped milk may be stored and administered to the infant via a feeding bottle or feeding tube depending on the situation. The mechanism of transfer of drugs in the breast milk has been extensively reviewed in the past (19,20). Drugs administered to the mother usually pass from the maternal plasma to the breast milk by passive diffusion where a column of milk remains in contact with lactocytes (21–23). Several factors affect transfer of drugs in the human milk: maternal plasma concentration of the drug, maternal plasma protein binding, drug ionization, drug lipid solubility, and drug molecular weight (19,24). Drugs highly bound to maternal plasma proteins are less likely to be transferred to breast milk (22,25). The lipid content in milk is variable not only from foremilk to hind milk but also during the day and even from breast to breast (23,26). Very few studies report separate drug concentrations in hind milk from foremilk (26). Because there is a delay in the occurrence of the side effect of a drug in an exposed infant (based on the pharmacokinetics in the exposed infant), differential concentration of the drug in foremilk and hind milk during a single feeding may perhaps not be an influential factor dictating the occurrence of side effects in the exposed infant.

The susceptibility of the baby to a drug that is secreted in human milk depends on the maternal dose, frequency of feeding, volume of milk ingested, the potential duration of action of the drug in the infant, and the maturity of the baby (19,24,25). The ideal drug would be one with high maternal protein binding, high degree of ionization, short half-life, poor oral bioavailability, and low lipid solubility. The magnitude of risk of exposure of the breast-fed infant to drugs in the maternal plasma has been described using various indices such as the milk-to-maternal plasma drug concentration (M : P ratio) and the 'exposure index' (24,25,27).

Method

A search of available literature was conducted using the PubMed database from the National Library of Medicine. The keywords used were anesthesia, breast-feeding, and the corresponding drug in question. The drugs included intravenous anesthetic agents–(propofol, thiopentone, etomidate, and ketamine); inhalational agents–(sevoflurane, isoflurane, halothane, desflurane, and nitrous oxide); opioid analgesics–(fentanyl, morphine, hydromorphone, hydrocodone, oxycodone, remifentanil, meperidine, and codeine); benzodiazepines–(diazepam, lorazepam, and midazolam); and nonsteroidal anti-inflammatory drugs (ibuprofen, ketorolac, and diclofenac); neuromuscular blocking agents; anticholinergic drugs (atropine and glycopyrrolate); anticholinesterases (neostigmine); antiemetics and local anesthetic agents. An additional literature search was also made via the LactMed website: http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT

The reviewed articles were graded based on the Levels of Evidence (LOE) and the strength of recommendation (SOR) grading followed by the Oxford Center for Evidence based Medicine (28; LOE Level 1 = randomized

© 2013 John Wiley & Sons Ltd

control trials, Level 2 = controlled nonrandomized trials, Level 3 = case control studies, Level 4 = case series and grade 5 for consensus or expert opinion; SOR level A = good evidence, B = moderate evidence, C = poor evidence, D = inconclusive studies). Please refer to the website: http://www.cebm.net/.

Drugs use in the perioperative period

The pharmacological effects of the various anesthetic and nonanesthetic drugs are described below.

Anesthetic drugs

Intravenous anesthetic agents

These include propofol, thiopentone, ketamine, and etomidate (29). The comparison of these drugs with regard to transfer into breast milk is shown in Table 1.

Propofol There is a case report of a 33-year-old woman who was administered propofol as a part of general anesthesia for laparoscopic removal of ectopic pregnancy. The woman reported bluish green breast milk pumped 8 h after surgery. The green color lasted for 48 h although there is no comment on the effect on the baby in that report (30). A study investigated the levels of propofol in breast milk and plasma of five lactating women who were administered propofol for general anesthesia. The study revealed that on an average 0.025% of the maternal propofol dose was detected in the breast milk (31). In that study, a 24-h breast milk collection was used for the study; none returned to the infant, hence possible clinical effects on the infant were not measured (31). A similar study also revealed very low concentration of propofol in the breast milk of women administered propofol for general anesthesia for cesarean section (32). The authors report no neurological signs of drug depression in the neonates (32).

Thiopentone Negligible concentrations of thiopentone were found in the breast milk (0.9 mcg·ml^{-1} in mature milk and 0.034 mcg·ml^{-1} in the colostrum respectively, milk/plasma ratio <1, [LOE 2]; 33). The authors concluded that these concentrations would be nontoxic to the nursing infant. In another study (LOE 2), in women undergoing cesarean section under general anesthesia, colostrum/plasma ratios of thiopentone at 4 and 9 h were 0.67 and 0.68, respectively (34). The mean concentrations of thiopentone in colostrum were 1.98 mg·ml^{-1} at 30 min, 0.91 mg·ml^{-1} at 4 h, and 0.59 mg·ml^{-1} at 9 h, respectively (34). They concluded that thiopentone may be administered in the lactating women (SOR B). This drug is not currently available in the United States because of the controversy over its use in capital punishment.

Table 1 Transfer of commonly used intravenous anesthetic agents in breast milk, NA, not available

Drug	Dose (mg kg^{-1})	Percentage transferred in breast milk	Milk or colostrum: plasma concentration ratio
Propofol (29–32)	1.5–2.5	0.025%	<1
Thiopentone (29,33,34)	3–5	NA	0.6
Etomidate (29,34)	0.2–0.4	NA	1.2 at 30 min
Ketamine (29)	1–2	NA	NA

Etomidate There are limited data available regarding etomidate in the setting of breast-feeding and anesthesia. In the study described above, the authors used either thiopentone (5 mg·kg^{-1}) or etomidate (0.3 mg·kg^{-1}) for induction of anesthesia for elective cesarean section (34). The colostrum/plasma etomidate ratio was 1.2 at 30 min. Etomidate was not detected in any of the 2-h maternal plasma samples but was still detectable in nine of 20 colostrum samples, with a mean value of 16.2 ng·ml^{-1} at 2 h. The authors concluded that a rapid decline in etomidate concentrations in colostrum would permit early feeding of the newborn after cesarean section (34). Based on this, the etomidate may be used in lactating women (LOE 2, SOR B).

Ketamine There are no published human studies regarding the transfer of ketamine to human milk. There is one study suggesting that ketamine administration may affect the motivation for breast-feeding in lactating rats (35). No conclusions can be drawn on the use of ketamine in lactating women and the effects on the infant.

Volatile anesthetic agents

There are no data related to actual levels measured in the human milk of women administered a volatile anesthetic agent. Desflurane or sevoflurane levels in milk most likely have no clinical importance 24 h after anesthesia due to rapid washout. There have been potential safety issues for occupational exposure to inhaled anesthetic gases (primarily nitrous oxide). The National Institute for Occupational Safety and Health Administration (NIOSH, Centers for Disease Control and Prevention, USA) recommends no worker be exposed to >2 ppm (ceiling concentrations) of the halogenated vapors over a period of 1 h (http://www.cdc.gov/niosh/docs/1970/77-140.html). The use of scavenging systems and minimizing the leaks and spills can help reduce potential risks.

© 2013 John Wiley & Sons Ltd

Use of xenon as an inhalational anesthetic gas has been described in recent years. Its advantage is its rapid onset and offset of action and its characteristics being close to an ideal anesthetic gas. However, its cost has been its limiting factor. This drug is not available for use in anesthesia in the USA. In a report describing the use of general anesthesia with propofol, remifentanil and xenon in four breast-feeding women, the xenon levels in the maternal milk were found to be zero immediately postextubation (36). Perhaps, in the future, use of xenon as a general anesthetic inhalational agent may prove beneficial to the breast-feeding mother with early return to breast-feeding as well as no effect on the breast-fed infant (36; LOE 3).

The ambient concentrations of nitrous oxide, sevoflurane, and desflurane in the operating room, recovery area, and the intensive care unit (ICU) areas have been reported in one study (37). Although, the concentration of all three agents was below the minimum working place concentrations (especially for nitrous oxide, 100 ppm, time weighted average 8 h, Prevention of Occupational Risks in Health services, Germany), it was above the threshold of 0.1 MAC for maternal protection (Maternal Protection Law, Germany) in the recovery area. The authors concluded that pregnant and breast-feeding women should not work in the recovery room area because of increased concentrations in these areas (37; LOE 2). In another report (LOE 4), the authors measured the concentration of halothane from a breast milk specimen from a lactating, practicing anesthesiologist (38). There was no scavenging system used for elimination of anesthetic gases from the operating room environment at that time. The concentration measured in milk was 2 ppm, which was consistent with the level in the operating room environment. The milk/gas partition coefficient varied between 2.3 and 1.4. The authors attributed this to the changing fat content in the breast milk and also whether or not halothane was measured in foremilk or hind milk (38). Based on the available evidence and the fact that the inhalational agents are rapidly excreted and have poor oral bioavailability, and with the use of scavenging systems in the operating rooms, volatile anesthetic agents may be safely used in lactating women (SOR C, D).

Opioid analgesics

The commonly used opioids and their transfer in breast milk are discussed below (Table 2).

Fentanyl The concentration of fentanyl in human milk has been studied (31). Following administration of 100 mcg of fentanyl, intravenously, at anesthetic induction, fentanyl concentrations were measured along with propofol and midazolam concentrations (LOE 2). The authors report that in a 24 h collection of milk, following administration of general anesthesia, 0.033% of the maternal fentanyl dose was noted in the breast milk. Breast-feeding is considered acceptable following single doses to the mother; however, there is no information available after multiple intravenous injections. In a study of 50 patients who were administered, single bolus doses of fentanyl (100 mcg) or sufentanil (10–50 mcg) epidurally for cesarean section under epidural anesthesia, the authors did not find any detectable level of the drug in the breast milk (39; LOE 1, SOR A). Based on available evidence, single doses of fentanyl during anesthesia or epidural fentanyl may be administered in lactating women.

Fentanyl for management of chronic pain Transdermal patch, transmucosal lozenge, buccal tablet (Fentora®), and buccal film (Onsolis™) are not recommended per manufacturer instructions in nursing women due to potential for infant sedation and/or respiratory depression. The use of transdermal fentanyl patch 100 $mcg \cdot h^{-1}$ in a pregnant woman throughout her pregnancy for treatment of chronic pain has been reported in the literature (40). The mother's milk fentanyl level was 6.4 $ng \cdot ml^{-1}$ and the infant's blood fentanyl level was undetectable suggesting use of the fentanyl patch may be an option in a nursing woman for treatment of chronic pain (40). Symptoms of opioid withdrawal may

Table 2 Transfer of perioperatively use opioids into human breast milk (15); NA, data not available

Drug	Maternal dose	M : P ratio	% of maternally administered dose found in colostrums or breast milk	Oral bioavailability
Morphine (15,41–46,49)	15 mg iv	1.1–3.6	0.8–12%	26%
Meperidine (15,49–56)	50–150 mg	0.82–1.59	NA	<50%
Fentanyl (15,39,40,49)	50–400 mcg iv	NA	0.033%	NA
Alfentanil (15,49)	50 $mcg \cdot kg^{-1}$ iv	NA	NA	NA

© 2013 John Wiley & Sons Ltd

occur in any infant whose mother has received chronic treatment with fentanyl. These symptoms may occur following the cessation of breast-feeding.

Morphine Morphine secretion in breast milk has been extensively studied in the literature. Morphine is transferred to human milk in small amounts. Morphine has an oral bioavailability of 30%; its active metabolite, morphine-6-glucuronide, has a bioavailability of 4%. It is important to note that morphine-6-glucuronide is also more potent and requires renal elimination. Plasma morphine concentration of 125 $ng \cdot ml^{-1}$ has been reported for adequate sedation in 50% of the neonates compared with a far lower concentration of 12 $ng \cdot ml^{-1}$ for cardiac surgery in older children (41,42; LOE 2b, SOR B).

Administration of a single dose of morphine to the mother is not expected to cause detrimental effects in nursing infants. However, there is considerable concern regarding the use of repeated doses of both morphine and codeine in breast-feeding mothers. In a study of five lactating women who were administered morphine, epidurally (4 mg) or parentally (intramuscularly or intravenously; 5–15 mg every 4–6 hourly), the peak morphine concentration in milk was found to be 82 $mcg \cdot l^{-1}$ at 30 min (82 $ng \cdot ml^{-1}$) after epidural administration and 500 $ng \cdot ml^{-1}$ (500 $mcg \cdot l^{-1}$) following parenteral administration (10-mg intravenous and 5-mg intramuscular; 43). The half-life of morphine in human breast milk was found to be 3 h. The authors suggest based on their findings that an exclusively breast-fed infant would receive 75 $mcg \cdot kg \cdot day^{-1}$ of morphine; <6% of the weight-adjusted maternal dose of morphine (43; LOE 2, SOR B). In fact, higher morphine concentrations in breast milk (100 $ng \cdot ml^{-1}$ in foremilk and 10 $ng \cdot ml^{-1}$ in hind milk) have been reported in case of a woman, 21 days postpartum, who received oral morphine, suggesting that the amount that an infant may receive is variable and may be much higher: that is, 0.8–12% of the maternal oral dose (44; LOE 4).

Morphine and morphine-6-glucuronide levels have been studied in the colostrum of seven postcesarean section women who were administered intravenous patient-controlled analgesia with morphine (45). The study reported milk (colostrum) morphine concentration ranging from <1 to 48 $ng \cdot ml^{-1}$ and of morphine-6-glucuronide from <5 to 1084 $ng \cdot ml^{-1}$. The safety of breast-feeding for infants whose mothers are on morphine patient-controlled analgesia is questionable (45; LOE 2).

Morphine for the management of chronic pain The administration of intrathecal morphine via a pump to the mother for chronic pain management resulted in minimal maternal serum and breast milk levels. In that case, the maternal milk concentrations were either undetectable or below the quantification sensitivity of the assay (46). Chronic use of morphine by a nursing mother may lead to higher levels of morphine in the infant especially in neonates or in infants with hepatic or renal dysfunction. Morphine should be used with caution in case of breast-feeding women. The very young infant is especially at risk for both acute and chronic opioid exposure.

Hydromorphone This analgesic is transferred to breast milk. In a study evaluating the pharmacokinetics of intranasally administered hydromorphone, the observed milk/plasma ratio was found to be 2.57 (47). The half-life of hydromorphone in maternal plasma was 11 h, and in milk, the half-life was 10.5 h. The authors estimated that the breast-fed infant would receive approximately 0.67% of the maternal dose of hydromorphone (adjusted for body weight; 47; LOE 2). The authors conclude that both passive diffusion and active transport are potential mechanisms of hydromorphone transfer into milk (47). There was no mention of any possible effect on the infant, but the long half-life in both maternal plasma and milk suggests that caution should be used especially with repeated maternal doses.

Hydrocodone In a pharmacokinetic study evaluating the excretion and effect of hydrocodone and hydromorphone in breast milk of 30 women, breast-fed neonates received ~1.6% (range was 0.2–9%) of the maternal weight-adjusted hydrocodone bitartrate dosage. When combined with hydromorphone, the total median opiate dosage from breast milk is 0.7% of a therapeutic dosage for older infants (48). The study also found that little to almost no hydromorphone was secreted into breast milk (48; LOE 2). In a case report by Anderson *et al*. two infants whose mothers who received hydrocodone along with acetaminophen received an estimated 3.1% and 3.7% of the maternal weight-adjusted dosage (48). The authors concluded that neonates and preterm infants may be more susceptible than older infants to adverse effects of hydrocodone and its metabolites in breast milk (LOE 4, SOR C; 48).

Remifentanil There are no published data on maternally administered remifentanil use and its effect on the breast-fed infant. However, it has a 'brief context sensitive' half-life of <10 min and hence may be considered safe for mothers of breast-fed infants (49). However, because of its short duration of action, it is not suitable for acute postoperative pain. Its use has been recently

© 2013 John Wiley & Sons Ltd

described for patient-controlled analgesia in labor (LOE 2, SOR B; 50).

Meperidine Meperidine has been a popular analgesic in obstetric practice. It has an active metabolite normeperidine (49). Analgesic blood levels of 100–150 $mcg{\cdot}ml^{-1}$ have been reported when used intramuscularly in cancer patients (51; LOE 1).When administered to the woman in labor, it can cause neonatal respiratory depression (15). The neonatal half-lives for meperidine and normeperidine are 13 and 63 h, respectively (52). Meperidine may be secreted in small amounts in breast milk. A wide range of levels of meperidine (36.2–314 $ng{\cdot}ml^{-1}$) and its metabolite normeperidine (0–333 $ng{\cdot}ml^{-1}$) in breast milk have been reported, when administered to women for postpartum analgesia (53). A higher incidence of neurobehavioral depression has been observed in neonates whose mothers received patient-controlled analgesia with meperidine in comparison with morphine (54; LOE 2). In that study, the authors also reported a normeperidine/meperidine ratio of 3 : 1 in the breast milk at 48 h (54). In a report of 20 women who were administered epidural meperidine via patient-controlled epidural analgesia, the combined absolute infant dose of meperidine and normeperidine was found to be 1.8% of the neonatal therapeutic dose (55; LOE 2). The authors concluded that infants who are breast-fed are at a low risk of exposure when mothers are administered meperidine epidurally than via patient-controlled epidural analgesia (55). In another study, investigators report a milk concentration of 176 $ng{\cdot}ml^{-1}$ in eight women who received 25 mg of meperidine intravenously for cesarean section with a milk/plasma ratio of 2.3 (range, 1.5–4.2; 56). In the same study, in another woman who received 50 mg of meperidine during anesthesia and 25 mg of meperidine 2 h later, the milk concentration was 571 $ng{\cdot}ml^{-1}$ after 4 h and 224 $ng{\cdot}ml^{-1}$ after 8 h (56; LOE 2). Available literature suggests that meperidine may not be a drug of choice in lactating women as there is a higher risk of respiratory depression in the breast-fed infant although epidural meperidine carries lower risk of infant side effects (SOR B).

Codeine Codeine is used for the treatment of moderate pain postoperatively**.** Codeine is secreted in breast milk because of its high lipophilicity and weak protein binding properties. Codeine is a prodrug, methyl morphine. It is metabolized to morphine by the hepatic microsomal enzyme system CYP2D6; an enzyme that catalyzes the demethylation reaction of codeine to morphine. There is a case report of a breast-fed neonate whose mother was prescribed a combination of codeine with acetaminophen for postepisiotomy pain (57; LOE 4). The infant was found to be lethargic with difficulty with breast-feeding on day 7 and died on day 13 after birth. The blood concentration of morphine (the active metabolite of codeine) was found to be 70 $ng{\cdot}ml^{-1}$; much higher than the levels of 0–2.2 $ng{\cdot}ml^{-1}$ typically found in this situation. Genetic analysis of the mother revealed the presence of CYP2D6*2A allele with CYP2D6*2 $\times$ 2 gene duplication, classified as ultra-rapid metabolizer (57). Breast-fed infants of mothers with combined genetic polymorphisms of the CYP2D6 and the UGT2B7 (incidence of 1.4% in Western European populations) appear to have an increased risk of severe neonatal depression upon maternal consumption of codeine (58). Based on this and other reports, the administration of codeine to the breast-feeding mother is best avoided regardless of the infant's age (58,59; LOE 3, SOR B).

Oxycodone A recent paper emphasizes the potential danger of the use of opioids in the breast-feeding mother. In that study, three groups of breast-feeding mothers and their infants were studied. Mothers in the three groups received oxycodone, codeine, or acetaminophen, respectively, for postpartum analgesia (60). Central nervous system (CNS) depression was measured by standardized questionnaires. Infant CNS depression occurred in 20.1% of oxycodone group, 16.7% in the codeine group, and 0.5% in the acetaminophen group. The fact that the mothers in the oxycodone and codeine groups whose infants were depressed took more medication than the mothers of the nondepressed infants in each group is important. Oxycodone has an active metabolite (oxymorphone), which is 14 times more potent than oxycodone because of its higher affinity for the mu-receptor (61). Oxycodone does not appear to be safer than codeine (LOE 2).

Tramadol Tramadol and its active metabolite, 0-desmethyltramadol, are excreted into breast milk. One study of 75 mothers given tramadol for postpartum pain showed average milk concentrations of 748 $mcg{\cdot}l^{-1}$ for tramadol and 203 $mcg{\cdot}l^{-1}$ for o-desmethyltramadol 6 h after the administration of 100 mg orally to the mothers. This would expose an infant to an average daily dosage of 112 $mcg{\cdot}kg^{-1}$ for tramadol and 30 $mcg{\cdot}kg^{-1}$ for the o-desmethyltramadol metabolite (62). These 75 infants were compared with another 75 infants whose mothers did not take tramadol, but did take other opiates and/or nonsteroidal anti-inflammatory drugs. No adverse clinical effects in the infants were observed. There was no difference between these two groups of infants with respect to the Neurologic and Adaptive Capacity Score (63). As with any infant whose mother is receiving an

© 2013 John Wiley & Sons Ltd

opioid, the infant should be observed for signs of respiratory depression, sedation, and decreased alertness.

Other opioid analgesics Pharmacokinetics of nalbuphine, butorphanol, and pentazocine with regard to breast milk has not been reported.

Benzodiazepines

Benzodiazepines are often used for sedation and anxiolysis (64). The most commonly used drugs are diazepam, lorazepam, and midazolam (64). Diazepam is longer acting compared with the other two drugs and has an active metabolite, desmethyl diazepam, which has a half-life of 30–100 h. Maternal use of diazepam is not suitable in labor as it may cause lower APGAR scores in the newborn infant. On the other hand, lorazepam has a shorter half-life compared with diazepam and does not have an active metabolite. Its effect on neonatal behavior is minimal in comparison with diazepam (65). Midazolam is 2–3 times more potent than diazepam and has become popular with anesthesiologists because of its water solubility, titrability, and rapid offset of action (Table 3).

Diazepam Diazepam is known to be transferred in breast milk. The milk/plasma ratios for diazepam and its active metabolite desmethyl diazepam have been reported to vary between 0.1–0.11 and 0.08–0.13, respectively (66,67). Undetectable levels of diazepam and its metabolite in the breast milk have been reported in one study (LOE 2; 56). In another study of nine women who were administered diazepam during the peripartum period, the levels of diazepam in the infant plasma were noted to persist for as long as 10 days (68; LOE 3). In a case report of a woman whose breast milk was studied during withdrawal from a combined diazepam and oxazepam therapy, diazepam (milk/plasma ratio 0.2) could not be detected in the infant's plasma, but low levels of N-desmethyl diazepam (milk/plasma ratio 0.13), temazepam (milk/plasma ratio 0.14), and oxazepam (milk/plasma ratio 0.1) were detected (69; LOE 4).

Lorazepam In a report of four breast-feeding women who received lorazepam 3.5 mg orally as a premedication 2 h prior to surgery, the concentration of lorazepam in breast milk was found to be 8–9 $ng \cdot ml^{-1}$ (70). This was found to be far less than the reported concentrations of 23–82 $ng \cdot ml^{-1}$ in the newborn as reported in another study; levels insufficient to cause neonatal neurobehavioral depression (65; LOE 4).

Midazolam In a study, five lactating women undergoing general anesthesia were administered midazolam premedication followed by general anesthesia with propofol and fentanyl (31). The investigators found that an average of 0.005% of the maternal midazolam dose was found in 24 h of milk collection, representing 0.009% of the elimination clearance (31). The authors concluded that the amount of midazolam (as well as propofol and fentanyl) excreted in breast milk is not a sufficient justification of interruption of breast-feeding (31; LOE 2). In a randomized study, investigators found that women who received 15 mg of oral midazolam, the milk/plasma ratio was found to be 0.15. The authors concluded based on their study, that very negligible midazolam is transferred via milk to the baby if the baby is nursed more than 4 h after the oral dose of midazolam (71; LOE 1).

Based on available evidence, use of midazolam either as premedication or intraoperatively under anesthesia may be considered safe in lactating women (SOR A, B). However, use of diazepam may be considered unsafe in terms of effects on the breast-fed infant. Lorazepam may be used, but with caution.

Nonsteroidal anti-inflammatory drugs (NSAIDS)

These groups of drugs have an opioid sparing effect and hence are popular in the acute postoperative pain setting. Ketorolac, administered intravenously, is frequently used in the intraoperative and the postoperative periods. The distribution of ketorolac in breast milk has been studied in ($n = 10$) women who were 2–6 days postpartum (72). Women were given ketorolac, orally, 10 mg, 4 $times \cdot day^{-1}$ for 2 days. Simultaneous breast milk and maternal serum samples were drawn four times over the dosing period and the following day (day 3). Breast milk concentrations of ketorolac ranged from 5.2 to 7.9 $ng \cdot ml^{-1}$. The milk/plasma ratio ranged from 0.015 to 0.037. The authors estimated the exposure of ketorolac to the breast-feeding infant to be 0.16% to 0.40% of the maternal dose (72; LOE 2). It is

Table 3 Transfer of perioperatively used benzodiazepines into human breast milk (15); NA, data not available

Drug	Maternal dose $mg \cdot day^{-1}$	Adult half-life hours	Pediatric half-life	Milk : Plasma ratio	Oral bioavailability (%)
Diazepam (15,64,67,68)	30	43	20–50	0.10–0.58	99
Lorazepam (15,64,65,70)	5	14	NA	0.15–0.26	90
Midazolam (15,64,71)	15	1.9	6.5–23	0.15	27

© 2013 John Wiley & Sons Ltd

recommended that NSAIDS with short half-lives, for example, propionic derivatives such as ibuprofen, may be used in lactating women (73). The amount of drug exposure to the infant may be minimized if the medication is taken by the mother at the time of breast-feeding so that the next feed is administered after a period of time that equals one half-life of the drug (73; LOE 4). Based on the current available evidence, NSAIDs may be used in lactating women (SOR B, C).

Neuromuscular blocking agents

These are quaternary ammonium compounds (74). They have a poor lipid solubility and are largely distributed in the extracellular fluid volume (74). They have poor oral bioavailability; hence, their administration may be considered safe for the breast-feeding infant. Suxamethonium has a rapid onset and offset of action. Based on these facts, that is, poor oral absorption, and a rapid elimination from maternal circulation, it is considered to be safe with regard to breast-feeding. The nondepolarizing agents used currently in clinical practice include atracurium, cisatracurium, rocuronium, and pancuronium. To date, there are no data on the pharmacokinetics of these drugs in breast milk. Based on poor oral bioavailability and poor lipid solubility, they may be considered safe for use in the breast-feeding mother (LOE 4, SOR D). As with any drug for which no data regarding pharmacokinetics in breast milk exists, close observation of the infant is necessary.

Drugs used for reversal

Typical agents used for reversal are anticholinesterase drugs, usually neostigmine in conjunction with an antimuscarinic drug such as atropine or glycopyrrolate to block the muscarinic effects of the anticholinesterase (75,76).

Anticholinergic agents Those commonly used by most anesthesiologists are atropine and glycopyrrolate (76). Atropine is a tertiary amine, known to be rapidly absorbed from the gastrointestinal tract and found in trace concentrations in the breast milk. Glycopyrrolate is a quaternary ammonium compound, which does not cross the central nervous system membrane barriers, hence not expected to be found in the breast milk. Also, it is poorly absorbed through the gastrointestinal tract (12). There are no human studies on the pharmacokinetics of these drugs in the human breast milk (12).

Anticholinesterases These include neostigmine, physostigmine, pyridostigmine, and edrophonium (76). These drugs are also used in the treatment of myasthenia gravis as well as for reversal of neuromuscular blockade for general anesthesia. Neostigmine is a quaternary ammonium compound with a half-life of 15–30 min. In a report of six breast-fed infants whose mothers were administered neostigmine for the treatment of myasthenia gravis, one newborn infant appeared to have abdominal cramps after a breast-feeding episode; efforts to detect neostigmine in breast milk failed (77; LOE 4). In a report of two infants whose mothers received pyridostigmine for the treatment of myasthenia gravis, the per kilogram dose of pyridostigmine ingested by the nursing infant was only 0.1% of that taken by the mother (maternal oral doses 180–300 $mg \cdot day^{-1}$) and was therefore considered safe for the breast-feeding infant (78; LOE 4, SOR D). There are no data on breast milk pharmacokinetics related to physostigmine and edrophonium.

Antiemetics

The commonly used antiemetics in the perioperative period include–metoclopramide, prochlorperazine, promethazine, and ondansetron.

Metoclopramide is an antiemetic and has been used as a galactogogue (17). In a report of five breast-fed infants whose mothers were administered oral metoclopramide, 10 mg, three times a day, for insufficient milk supply, the serum metoclopramide levels were undetectable (<2 $mcg \cdot ml^{-1}$) in four infants. In the fifth infant, the serum levels were 20.9 and 18.6 $mcg \cdot ml^{-1}$ at 4 and 14 days postpartum, averaging 8% of the mother's serum levels (LOE 2; 79). There are no reported data on the use of the remaining drugs mentioned above with regard to pharmacokinetics in breast milk or effects on the infant. Metoclopramide and ondansetron (due to absence of sedative side effects) may be safely used in lactating women.

Local anesthetics

The most commonly used local anesthetics are lidocaine, bupivacaine, and ropivacaine (80). These amino amide compounds are lipid-soluble (80). They may be secreted in small amounts in breast milk. The effect will depend on the route and duration of administration. Previous studies have shown a negative association of labor epidural analgesia and early successful breast-feeding (81). In a randomized controlled study on 30 parturients who either received or did not receive epidural analgesia for postoperative pain following cesarean section, the investigators found that the women in the epidural group had improved breast-feeding and infant weight gain (LOE 1; 82). However, in that study, the authors used epidural bupivacaine without narcotics and did not measure milk production or bupivacaine levels in the breast milk

© 2013 John Wiley & Sons Ltd

(82,83). In a case report of a 33-year-old breast-feeding mother who underwent cholecystectomy, the authors administered a continuous intrapleural infusion of bupivacaine 0.25% at the rate 0.13 $ml \cdot kg \cdot h^{-1}$ (83). The authors estimated that the infant received 0.1% of the maternal dose of bupivacaine and concluded that it was safe for the breast-fed infant (LOE 4; 83). Excretion of bupivacaine and lidocaine in the breast milk has been reported following epidural anesthesia for cesarean section (84). Blood and milk samples were collected at 2, 6, and 12 h. The study indicated that lidocaine, bupivacaine, and their metabolite 2,6-pipecoloxylidide were excreted in breast milk (84). The authors reported milk/serum ratio of 1.07 ± 0.82, 0.34 ± 0.24, and 1.37 ± 0.61 (mean $\pm$ SD) for lidocaine, bupivacaine, and pipecolylxylidide, respectively (84). The authors concluded that the use of both lidocaine and bupivacaine was safe with regard to breast-feeding (LOE 2, SOR B; 84). A study by Giuliani *et al*. also suggested the safety of use of lidocaine for local anesthesia for dental extractions in case of breast-feeding women (85; LOE 2). Local anesthetics especially lidocaine, bupivacaine, and ropivacaine may be safely used in lactating women.

Management of anesthesia in the breast-feeding mother

Preoperative preparation

This is a unique situation where one has to consider two patient entities in one–mother and the breast-fed baby (Appendix 1). Hence, in addition to a thorough history, clinical examination and investigations where appropriate, in case of a breast-feeding mother, a history regarding breast-feeding, intention to breast-feed in the postoperative period, drug history as well as the infant's birth history and developmental history must be obtained. The surgery may be scheduled such that the infant may be breast-fed just prior to the procedure. A prolonged period of preoperative fasting should be avoided and an intravenous infusion of fluids may be considered to avoid dehydration in the breast-feeding patient who is awaiting surgery. During the preoperative visit, it should be explained that although attempts will be made to administer drugs with low transferability in the breast milk, there will still be some amount of the drug(s) transferred to the breast milk. The amounts are thought to be clinically insignificant, but the mother should be assured that the infant will be closely monitored. The choice of the anesthetic technique, advantages of regional, or central neural blockade, and strategies for postoperative pain management should also be clarified and discussed.

Selection of Anesthetic Technique

This will also depend on the type and site of surgery as well as the comfort level of the patient. Local anesthesia, regional anesthesia, and central neural blockade may be used as sole techniques or in combination with general anesthesia. The advantages of nerve blocks or central neural blockade (spinal or epidural anesthetic) include faster recovery from anesthesia and return to baseline status so that the mother is able to breast-feed sooner albeit decreasing the need for intravenous narcotics, benzodiazepines, and anesthetic induction agents. Also, with these techniques, there is a lower incidence of postoperative nausea and vomiting compared with general anesthesia and extended pain relief, thereby minimizing the narcotic analgesic requirement in the postoperative period. Certainly, available literature although slightly conflicting, largely suggests the early return to and longer duration of breast-feeding in women who received epidural anesthesia in comparison to general anesthesia (86–88).

General anesthesia plan

Midazolam or lorazepam should be the choice for sedative premedication. Propofol, thiopentone, or etomidate may be safely used; although there is no literature on the impact of ketamine on the breast-feeding and its effects on the infant. For maintenance of anesthesia, nitrous oxide, sevoflurane, isoflurane, or desflurane may be considered safe. Neuromuscular blockade may be safely facilitated with the currently used drugs including suxamethonium, rocuronium and atracurium, or cisatracurium. Reversal agents may also be safely administered. Antiemetics should be those with minimal sedative effects such as ondansetron and dexamethasone although routine antiemetics have not been found to impact the breast-fed infant. During the entire procedure, the mother should be well hydrated. The aim should be to use short acting agents to facilitate smooth early recovery of the breast-feeding mother and maximize use of nonnarcotic nonsedative analgesic and use of local anesthetic agents where possible to facilitate postoperative analgesia.

Options in case mother wants to temporarily suspend breast-feeding

These include pumping and storing the milk prior to the procedure; the baby can be bottle-fed with previously stored breast milk or pumping and discarding breast milk postanesthesia for 24 h ('pump and dump') and then resuming to breast-feeding (22). Because the

© 2013 John Wiley & Sons Ltd

exposure of the infant over 24 h to most drugs transferred to breast milk is rarely >1–2% of the original maternal dose (89), some anesthesiologists make the recommendation to resume breast-feeding when sufficiently recovered from anesthesia. There are no scientific data to support postoperative 'dumping' unless the mother is not awake enough to breast-feed in which case she may feel too weak to pump!

Discussion/conclusion

All the drugs administered to the mother are secreted in breast milk thereby exposing the nursing infant to the possible adverse effects of that particular drug. The adverse effect of maternally administered drugs on the breast-fed infant depends on a multitude of factors. These factors include the type of drug, the amount of milk ingested by the breast-fed infant, age and maturity of the infant (15,20,90). Adverse drug reactions in breast-fed infants following maternal drug exposure are rare; most being minor incidents and notably in infants <2 months of age (91,92). The aim should be to minimize the exposure of the nursing infant to the drug. In general, the characteristics of an ideal drug for a breast-feeding woman are (1) the drug is minimally secreted or transported in breast milk, (2) the drug has a short elimination half-life, and (3) the drug should have inactive metabolites.

The anesthetic technique of choice depends on the type of surgery (major or minor procedure), urgency of surgery (emergency or elective), site of surgery, and the experience of the anesthesiologist. The aim should be to minimize the use of narcotics and benzodiazepines, use shorter acting agents and avoid agents, which have active metabolites. Often, the breast-feeding mother undergoing a surgical procedure is advised to discontinue breast-feeding in the postoperative period. However, with the advent of newer anesthetic agents and the available literature, this practice seems unnecessary and is in fact disadvantageous to the nursing infant (12,15,90). Indeed, the current literature suggests that although anesthetic drugs are transferred into the breast milk, the amount transferred is clinically insignificant and poses little or no risk to the nursing infant. Administration of anesthesia entails acute administration of drugs with potential for sedation and respiratory effects on the nursing infant. However, the short-term use of these drugs minimizes the possibility of these effects. Ideally, it would be appropriate for the mother to breast-feed the baby as soon as she feels alert and comfortable. Frequent clinical assessments of the nursing infant are important to identify the occurrence of any adverse effects on the baby. We suggest that breast-fed infants of mothers in the postanesthesia period or those on treatment with respiratory depressant drugs, be clinically monitored (especially in case of premature babies). Because there are no established standardized guidelines, each case may be judged on an individual basis. Perhaps, the clinical monitoring of the breast-fed infant, in extreme cases, may involve use of a pulse oximeter or apnea monitor; although this will also have implications on the utilization and combination of the adult and pediatric team resources. Further research in this direction will be useful in helping clinicians manage the mother and the breast-fed baby in the postoperative period. As the recent reports of adverse effects on infants from maternal opioid use illustrate, even single case reports must increase awareness of potential significant effects on the nursing infant regardless of drug class. A useful resource for the current literature on the use of drugs during lactation is LactMed (http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT). This database, sponsored by the USA National Library of Medicine, is a peer-reviewed, continually updated list of drugs and their levels in breast milk, effects on the nursing infant (if any), and any effect on lactation.

Finally, each case should be judged on its own merit and a team approach with good communication between the anesthesiologist, surgeon, and pediatrician is important for safe management of the breast-fed infant whose mother is administered anesthesia for surgical procedures.

Financial support

Department of Anesthesiology, Penn State Milton S Hershey Medical Center.

Conflict of interest

No conflicts of interest declared.

References

1 Rautava S, Walker WA. Academy of Breastfeeding Medicine founder's lecture 2008: breastfeeding–an extrauterine link between mother and child. *Breastfeed Med* 2009; **4**: 3–10.

2 Lawrence PB. Breast milk. Best source of nutrition for term and preterm infants. *Pediatr Clin North Am* 1994; **41**: 925–941.

3 Eidelman AI, Schanler RJ. American Academy of Pediatric section on breast feeding: breastfeeding and the Use of Human Milk. *Pediatrics* 2012; **129**: e827–e841.

4 Gartner LM, Morton J, Lawrence RA *et al.* Breastfeeding and the use of human milk. *Pediatrics* 2005; **115**: 496–506.

© 2013 John Wiley & Sons Ltd

5 Heird WC. Progress in promoting breastfeeding, combating malnutrition, and composition and use of infant formula, 1981–2006. *J Nutr* 2007; **137**: 499S–502S.

6 Labbok MH, Clark D, Goldman AS. Breastfeeding: maintaining an irreplaceable immunological resource. *Nat Rev Immunol* 2004; **4**: 565–572.

7 Ruiz-Palacios GM, Calva JJ, Pickering LK *et al*. Protection of breast-fed infants against Campylobacter diarrhea by antibodies in human milk. *J Pediatr* 1990; **116**: 707–713.

8 Xanthou M, Bines J, Walker WA. Human milk and intestinal host defense in newborns: an update. *Adv Pediatr* 1995; **42**: 171–208.

9 Gillman MW, Rifas-Shiman SL, Camargo CA Jr *et al*. Risk of overweight among adolescents who were breastfed as infants. *JAMA* 2001; **285**: 2461–2467.

10 Labbok MH, Hight-Laukaran V, Peterson AE *et al*. Multicenter study of the Lactational Amenorrhea Method (LAM): I. Efficacy, duration, and implications for clinical application. *Contraception* 1997; **55**: 327–336.

11 Clavano NR. Mode of feeding and its effect on infant mortality and morbidity. *J Trop Pediatr* 1982; **28**: 287–293.

12 Lee JJ, Rubin AP. Breast feeding and anaesthesia. *Anaesthesia* 1993; **48**: 616–625.

13 Lang C, Geldner G, Wulf H. Anesthesia in the breast feeding period. Excretion of anesthetic agents and adjuvants into breast milk and potential pharmacological side-effects on the suckling infant. *Anaesthesist* 2003; **52**: 934–946.

14 Bond GM, Holloway AM. Anaesthesia and breast-feeding–the effect on mother and infant. *Anaesth Intensive Care* 1992; **20**: 426–430.

15 Hale TW. Anesthetic medications in breastfeeding mothers. *J Hum Lact* 1999; **15**: 185–194.

16 Lawrence RA, Lawrence RM. Physiology of Lactation. 7th edn, Chapter 3. Maryland Heights, MO: Elsevier Mosby, Inc, 2011: 62–97.

17 Anderson PO, Valdes V. A critical review of pharmaceutical galactagogues. *Breastfeed Med* 2007; **2**: 229–242.

18 Sachs HC. The transfer of drugs and therapeutics into human breast milk: an update on selected topics. *Pediatrics* 2013; **132**: e796–e809.

19 Wilson JT, Brown RD, Cherek DR *et al*. Drug excretion in human breast milk: principles, pharmacokinetics and projected consequences. *Clin Pharmacokinet* 1980; **5**: 1–66.

20 Hale TW. Maternal medications during breastfeeding. *Clin Obstet Gynecol* 2004; **47**: 696–711.

21 Ito S, Lee A. Drug excretion into breast milk – overview. *Adv Drug Deliv Rev* 2003; **55**: 617–627.

22 Bowes WA Jr. The effect of medications on the lactating mother and her infant. *Clin Obstet Gynecol* 1980; **23**: 1073–1080.

23 Lawrence RA, Lawrence RM. Medications, Herbal Preparations, and Natural Products in Breast Milk. 7th edn, Chapter 12. Maryland Heights, MO: Elsevier Mosby, Inc, 2011: 364–405.

24 Atkinson HC, Begg EJ, Darlow BA. Drugs in human milk. Clinical pharmacokinetic considerations. *Clin Pharmacokinet* 1988; **14**: 217–240.

25 Anderson PO. Drug use during breast-feeding. *Clin Pharm* 1991; **10**: 594–624.

26 Lawrence RA, Lawrence RM. Biochemistry of Human Milk. 7th edn, Chapter 4. Maryland Heights, MO: Elsevier Mosby, Inc, 2011: 98–152.

27 Ito S, Koren G. A novel index for expressing exposure of the infant to drugs in breast milk. *Br J Clin Pharmacol* 1994; **38**: 99–102.

28 Horlocker TT, Brown DR. Evidence-based medicine: haute couture or the emperor's new clothes? *Anesth Analg* 2005; **100**: 1807–1810.

29 Sear JW. Essential drugs in anesthetic practice: clinical pharmacology of intravenous anesthetics. In: Alex Evers MM, Evan K, eds. Anesthetic Pharmacology: Basic Principles and Clinical Practice, 2nd edn. Cambridge, UK: Cambridge University Press, 2011: 444–465.

30 Birkholz T, Eckardt G, Renner S *et al*. Green breast milk after propofol administration. *Anesthesiology* 2009; **111**: 1168–1169.

31 Nitsun M, Szokol JW, Saleh HJ *et al*. Pharmacokinetics of midazolam, propofol, and fentanyl transfer to human breast milk. *Clin Pharmacol Ther* 2006; **79**: 549–557.

32 Dailland P, Cockshott ID, Lirzin JD *et al*. Intravenous propofol during cesarean section: placental transfer, concentrations in breast milk, and neonatal effects. A preliminary study. *Anaesthesiology* 1989; **71**: 827–834.

33 Andersen LW, Qvist T, Hertz J *et al*. Concentrations of thiopentone in mature breast milk and colostrum following an induction dose. *Acta Anaesthesiol Scand* 1987; **31**: 30–32.

34 Esener Z, Sarihasan B, Guven H *et al*. Thiopentone and etomidate concentrations in maternal and umbilical plasma, and in colostrum. *Br J Anaesth* 1992; **69**: 586–588.

35 Yamamuro Y. Exposure to common anesthetic agents alters pup-retrieval response in lactating rats. *Exp Anim* 2005; **54**: 369–372.

36 Stuttmann R, Schafer C, Hilbert P *et al*. The breast feeding mother and xenon anaesthesia: four case reports. Breast feeding and xenon anaesthesia. *BMC Anesthesiol* 2010; **10**: 1.

37 Byhahn C, Lischke V, Westphal K. Occupational exposure in the hospital to laughing gas and the new inhalation anesthetics desflurane and sevoflurane. *Dtsch Med Wochenschr* 1999; **124**: 137–141.

38 Cote CJ, Kenepp NB, Reed SB *et al*. Trace concentrations of halothane in human breast milk. *Br J Anaesth* 1976; **48**: 541–543.

39 Madej TH, Strunin L. Comparison of epidural fentanyl with sufentanil. Analgesia and side effects after a single bolus dose during elective caesarean section. *Anaesthesia* 1987; **42**: 1156–1161.

40 Cohen RS. Fentanyl transdermal analgesia during pregnancy and lactation. *J Hum Lact* 2009; **25**: 359–361.

41 Chay PC, Duffy BJ, Walker JS. Pharmacokinetic-pharmacodynamic relationships of morphine in neonates. *Clin Pharmacol Ther* 1992; **51**: 334–342.

42 Lynn AM, Opheim KE, Tyler DC. Morphine infusion after pediatric cardiac surgery. *Crit Care Med* 1984; **12**: 863–866.

43 Feilberg VL, Rosenborg D, Broen Christensen C *et al*. Excretion of morphine in human breast milk. *Acta Anaesthesiol Scand* 1989; **33**: 426–428.

44 Robieux I, Koren G, Vandenbergh H *et al*. Morphine excretion in breast milk and resultant exposure of a nursing infant. *J Toxicol Clin Toxicol* 1990; **28**: 365–370.

45 Baka NE, Bayoumeu F, Boutroy MJ *et al*. Colostrum morphine concentrations during postcesarean intravenous patient-controlled analgesia. *Anesth Analg* 2002; **94**: 184–187, table of contents.

46 Oberlander TF, Robeson P, Ward V *et al*. Prenatal and breast milk morphine exposure following maternal intrathecal morphine treatment. *J Hum Lact* 2000; **16**: 137–142.

47 Edwards JE, Rudy AC, Wermeling DP *et al*. Hydromorphone transfer into breast milk after intranasal administration. *Pharmacotherapy* 2003; **23**: 153–158.

48 Sauberan JB, Anderson PO, Lane JR *et al*. Breast milk hydrocodone and hydromorphone levels in mothers using hydrocodone for postpartum pain. *Obstet Gynecol* 2011; **117**: 611–617.

49 Stoelting RK, Hillier SC. Opioid agonists and antagonists. In: Stoelting RK, Hillier SC eds. Pharmacology & Physiology in Anesthetic Practice, 4th edn. Philadelphia: Lippincott Williams & Williams, 2006: 87–126.

50 Douma MR, Verwey RA, Kam-Endtz CE *et al*. Obstetric analgesia: a comparison of patient-controlled meperidine, remifentanil, and fentanyl in labour. *Br J Anaesth* 2010; **104**: 209–215.

51 Stambaugh JE Jr, Lane C. Analgesic efficacy and pharmacokinetic evaluation of meperidine and hydroxyzine, alone and in combination. *Cancer Invest* 1983; **1**: 111–117.

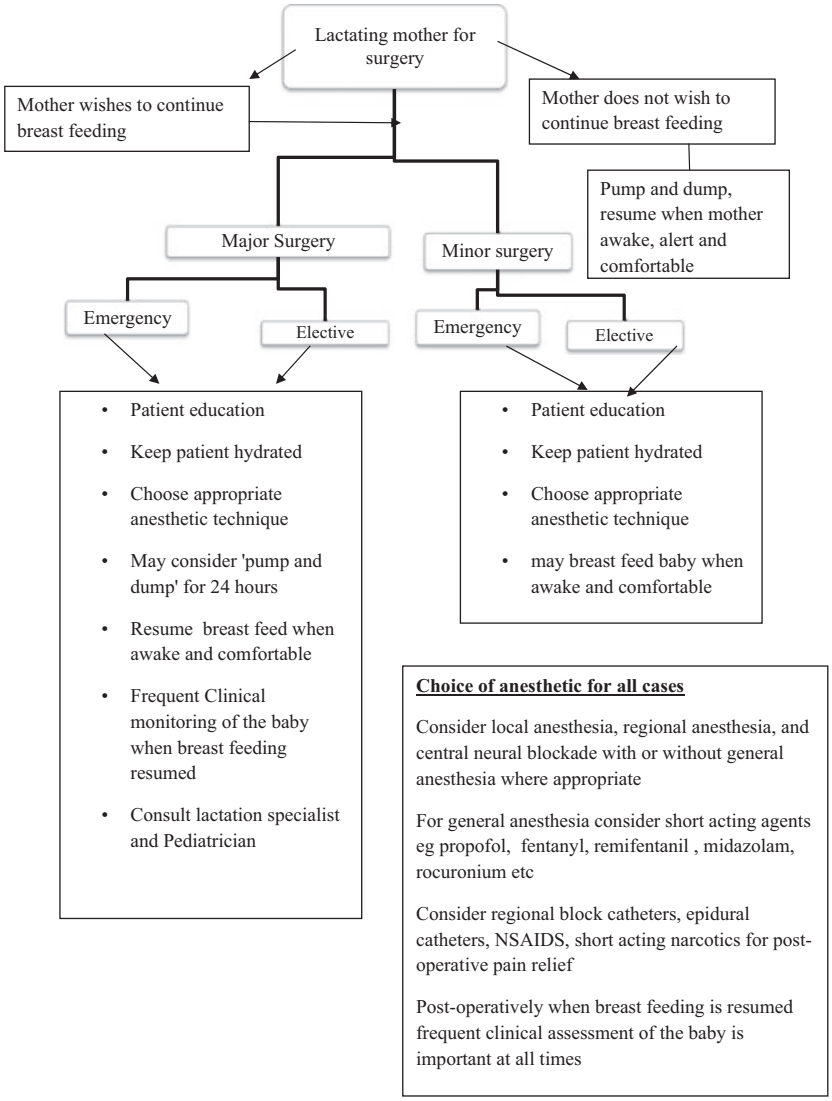
52 Kuhnert BR, Kuhnert PM, Philipson EH *et al*. Disposition of meperidine and

© 2013 John Wiley & Sons Ltd

normeperidine following multiple doses during labor. II. Fetus and neonate. *Am J Obstet Gynecol* 1985; **151**: 410–415.
53 Quinn PG, Kuhnert BR, Kaine CJ *et al*. Measurement of meperidine and normeperidine in human breast milk by selected ion monitoring. *Biomed Environ Mass Spectrom* 1986; **13**: 133–135.
54 Wittels B, Scott DT, Sinatra RS. Exogenous opioids in human breast milk and acute neonatal neurobehavior: a preliminary study. *Anesthesiology* 1990; **73**: 864–869.
55 Al-Tamimi Y, Ilett KF, Paech MJ *et al*. Estimation of infant dose and exposure to pethidine and norpethidine via breast milk following patient-controlled epidural pethidine for analgesia post caesarean delivery. *Int J Obstet Anesth* 2011; **20**: 128–134.
56 Borgatta L, Jenny RW, Gruss L *et al*. Clinical significance of methohexital, meperidine, and diazepam in breast milk. *J Clin Pharmacol* 1997; **37**: 186–192.
57 Koren G, Cairns J, Chitayat D *et al*. Pharmacogenetics of morphine poisoning in a breastfed neonate of a codeine-prescribed mother. *Lancet* 2006; **368**: 704.
58 Madadi P, Ross CJ, Hayden MR *et al*. Pharmacogenetics of neonatal opioid toxicity following maternal use of codeine during breastfeeding: a case-control study. *Clin Pharmacol Ther* 2009; **85**: 31–35.
59 Berlin CM Jr, Paul IM, Vesell ES. Safety issues of maternal drug therapy during breastfeeding. *Clin Pharmacol Ther* 2009; **85**: 20–22.
60 Lam J, Kelly L, Ciszkowski C *et al*. Central nervous system depression of neonates breastfed by mothers receiving oxycodone for postpartum analgesia. *J Pediatr* 2012; **160**: 33–37.
61 van den Anker JN. Is it safe to use opioids for obstetric pain while breastfeeding? *J Pediatr* 2012; **160**: 4–6.
62 Ilett KF, Paech MJ, Page-Sharp M *et al*. Use of a sparse sampling study design to assess transfer of tramadol and its O-desmethyl metabolite into transitional breast milk. *Br J Clin Pharmacol* 2008; **65**: 661–666.
63 Amiel-Tison C, Barrier G, Shnider SM *et al*. A new neurologic and adaptive capacity scoring system for evaluating obstetric medications in full-term newborns. *Anesthesiology* 1982; **56**: 340–350.
64 Stoelting RK, Hillier SC. Benzodiazepines (chapter 5). In: Stoelting RK, Hillier SC, eds. Pharmacology and Physiology in Anesthetic Practice, 4th edn. Philadelphia: Lippincott Williams & Williams, 2006: 140–154.
65 McBride RJ, Dundee JW, Moore J *et al*. A study of the plasma concentrations of lorazepam in mother and neonate. *Br J Anaesth* 1979; **51**: 971–978.
66 Patrick MJ, Tilstone WJ, Reavey P. Diazepam and breast-feeding. *Lancet* 1972; **1**: 542–543.
67 Erkkola R, Kanto J. Diazepam and breast-feeding. *Lancet* 1972; **1**: 1235–1236.
68 Cole AP, Hailey DM. Diazepam and active metabolite in breast milk and their transfer to the neonate. *Arch Dis Child* 1975; **50**: 741–742.
69 Dusci LJ, Good SM, Hall RW *et al*. Excretion of diazepam and its metabolites in human milk during withdrawal from combination high dose diazepam and oxazepam. *Br J Clin Pharmacol* 1990; **29**: 123–126.
70 Summerfield RJ, Nielsen MS. Excretion of lorazepam into breast milk. *Br J Anaesth* 1985; **57**: 1042–1043.
71 Matheson I, Lunde PK, Bredesen JE. Midazolam and nitrazepam in the maternity ward: milk concentrations and clinical effects. *Br J Clin Pharmacol* 1990; **30**: 787–793.
72 Wischnik A, Manth SM, Lloyd J *et al*. The excretion of ketorolac tromethamine into breast milk after multiple oral dosing. *Eur J Clin Pharmacol* 1989; **36**: 521–524.
73 Needs CJ, Brooks PM. Antirheumatic medication during lactation. *Br J Rheumatol* 1985; **24**: 291–297.
74 Stoelting RK, Hillier SC. Neuromuscular-blocking drugs (chapter 8). In: Stoelting RK, Hillier SC, eds. Pharmacology & Physiology in Anesthetic Practice, 4th edn. Philadelphia: Lippincott Williams & Williams, 2006: 208–250.
75 Stoelting RK, Hillier SC. Anticholinesterase drugs and cholinergic agonists (chapter 9). In: Stoelting RK, Hillier SC, eds. Pharmacology & Physiology in Anesthetic Practice, 4th edn. Philadelphia: Lippincott Williams & Williams, 2006: 251–265.
76 Stoelting RK, Hillier SC. Anticholinergic drugs (chapter 10). In: Stoelting RK, Hillier SC, eds. Pharmacology & Physiology in Anesthetic Practice, 4th edn. Philadelphia: Lippincott Williams & Williams, 2006: 266–275.
77 Fraser D, Turner JW. Myasthenia gravis and pregnancy. *Proc R Soc Med* 1963; **56**: 379–381.
78 Hardell LI, Lindstrom B, Lonnerholm G *et al*. Pyridostigmine in human breast milk. *Br J Clin Pharmacol* 1982; **14**: 565–567.
79 Kauppila A, Arvela P, Koivisto M *et al*. Metoclopramide and breast feeding: transfer into milk and the newborn. *Eur J Clin Pharmacol* 1983; **25**: 819–823.
80 Stoelting RK, Hillier SC. Local anesthetics (chapter 7). In: Stoelting RK, Hillier SC, eds. Pharmacology & Physiology in Anesthetic Practice, 4th edn. Philadelphia: Lippincott Williams & Williams, 2006: 179–207.
81 Baumgarder DJ, Muehl P, Fischer M *et al*. Effect of labor epidural anesthesia on breast-feeding of healthy full-term newborns delivered vaginally. *J Am Board Fam Pract* 2003; **16**: 7–13.
82 Hirose M, Hara Y, Hosokawa T *et al*. The effect of postoperative analgesia with continuous epidural bupivacaine after cesarean section on the amount of breast feeding and infant weight gain. *Anesth Analg* 1996; **82**: 1166–1169.
83 Baker PA, Schroeder D. Interpleural bupivacaine for postoperative pain during lactation. *Anesth Analg* 1989; **69**: 400–402.
84 Ortega D, Viviand X, Lorec AM *et al*. Excretion of lidocaine and bupivacaine in breast milk following epidural anesthesia for cesarean delivery. *Acta Anaesthesiol Scand* 1999; **43**: 394–397.
85 Giuliani M, Grossi GB, Pileri M *et al*. Could local anesthesia while breast-feeding be harmful to infants? *J Pediatr Gastroenterol Nutr* 2001; **32**: 142–144.
86 Lie B, Juul J. Effect of epidural vs. general anesthesia on breastfeeding. *Acta Obstet Gynecol Scand* 1988; **67**: 207–209.
87 Kiehl EM, Anderson GC, Wilson ME *et al*. Social status, mother-infant time together, and breastfeeding duration. *J Hum Lact* 1996; **12**: 201–206.
88 Halpern SH, Levine T, Wilson DB *et al*. Effect of labor analgesia on breastfeeding success. *Birth* 1999; **26**: 83–88.
89 Berlin CM Jr. Pharmacologic considerations of drug use in the lactating mother. *Obstet Gynecol* 1981; **58**: 17S–23S.
90 Montgomery A, Hale TW. ABM clinical protocol #15: analgesia and anesthesia for the breastfeeding mother. *Breastfeed Med* 2006; **1**: 271–277.
91 Anderson PO, Pochop SL, Manoguerra AS. Adverse drug reactions in breastfed infants: less than imagined. *Clin Pediatr (Phila)* 2003; **42**: 325–340.
92 Ito S, Blajchman A, Stephenson M *et al*. Prospective follow-up of adverse reactions in breast-fed infants exposed to maternal medication. *Am J Obstet Gynecol* 1993; **168**: 1393–1399.

© 2013 John Wiley & Sons Ltd

Appendix 1 Management of the lactating mother in the perioperative period.



© 2013 John Wiley & Sons Ltd