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REVIEW ARTICLE

Breast feeding and anaesthesia

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Summary

Anaesthetists require a good knowledge of the excretion of drugs in breast milk and the potential hazards to suckling infants of drug ingestion via breast milk. A brief account of the physiology of lactation is given. The mechanisms of drug passage into breast milk are discussed followed by a review of the excretion in breast milk of drugs used in anaesthetic practice. Suggestions for the management of anaesthesia in breast feeding mothers are offered.

Key words

Pharmacokinetics; distribution.

The recommended age for weaning of babies from breast feeding usually varies from 4–12 months in Western countries, but may be 18–24 months or even more in less developed countries [1]. With a growing appreciation of the benefits of breast feeding in recent years [2], it is common for anaesthetists to encounter nursing mothers who invariably question whether breast feeding after anaesthesia can harm their infants. Anaesthetists searching for information on the excretion of anaesthetic drugs in breast milk, and their potential hazards to suckling infants, are often unsuccessful in finding it in the standard anaesthetic textbooks and only find limited data on clinical experience in the literature. This review aims to collate and provide currently available information, and is designed to stimulate more interest and research to expand present knowledge.

Physiology of normal lactation

Each breast consists of 15 to 20 lobes, subdivided into lobules, which contain functional units composed of the alveoli (secretory apparatus), ducts, myoepithelial cells which surround the alveoli and ducts, nerves and the blood supply. During pregancy, oestrogen and progesterone stimulate further development of the breast tissue but inhibit the lactogenic influence of prolactin on the mammary glands. Delivery of the placenta removes the oestrogen and progesterone inhibition and prolactin, the plasma concentration of which rises throughout pregnancy, is free to stimulate the production of milk. Lactation itself is triggered by suckling which markedly stimulates the release of prolactin and oxytocin, both of which promote milk production and expression. Suckling also empties the breast of milk and directly encourages further lactation [3].

Mechanisms of drug passage into breast milk

These have been the subject of extensive review [3–6], and only a summary is presented here. The physicochemical and pharmacokinetic principles involved in the passage of drugs into breast milk are now reasonably well established. Factors governing the dose received by the infant, and the plasma level achieved in the infant, are complex and may be considered under three headings: maternal pharmacokinetics; mammary pharmacokinetics; infant pharmacokinetics.

Maternal pharmacokinetics

The maternal plasma concentration of a drug, that is, its presentation to the breast for secretion in milk, depends upon its pharmacokinetics. It depends on factors such as dose, route and frequency of administration, plasma protein binding, volume of distribution (Vd), metabolism and clearance. For drugs with a large Vd (e.g. highly lipid-soluble drugs) most of the drug is outside the plasma compartment, leaving only a small proportion free to transfer from plasma to milk. The extent of protein binding is also an important factor since only the free unbound drug is available for diffusion into breast milk. The free fraction of certain drugs (e.g. diazepam and salicylic acid)

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increases during pregnancy and for 1–5 days postpartum, and returns to normal about 5–7 weeks later [7]. Hence, altered drug disposition during late pregnancy and lactation may result in toxic drug levels in maternal plasma and milk.

Mammary pharmacokinetics

The milk-to-plasma (M/P) ratio of drug concentration may be used to estimate the dose of a drug in breast milk as a function of the maternal plasma concentration. It may be expressed in two ways: (i) the concentration in milk relative to that in plasma and (ii) more accurately, the area under the concentration–time curve in milk relative to that in plasma. Such measurements of the extent of drug transfer depend upon the transport mechanisms across biological membranes, physicochemical characteristics of the drug, pH of milk and distribution of the drug in milk.

Nonionised (lipid-soluble) drugs enter the breast milk from maternal plasma by passive diffusion down a concentration gradient. It involves the passage through multiple structures, which act as a semipermeable lipid barrier. The drug has to permeate multiple lipoprotein cell membranes: capillary endothelium, myoepithelial cell and mammary alveolar cell membrane, to reach the milk in the alveolar lumen. Although active or facilitated transport mechanisms have been described for some endogenous substances, there is no evidence to support the passage of drugs into human milk by these processes.

The principal physicochemical properties of a drug which determine the extent of drug transfer into breast milk are the pKa, partition coefficient (relative solubilities in fat and water) and molecular weight. Human milk has a mean pH of 7.09 which is lower than the plasma [8], resulting in different drug dissociation and unequal total concentrations of drugs in the two media. As a general rule, weak acids achieve a lower concentration in milk than in plasma (M/P ratio < 1.0) whereas weak bases achieve a higher M/P ratio (> 1.0). Therefore, in the case of a basic drug, only the nonionised fraction diffuses across the lipid membranes into milk, where more drug becomes ionised and hence 'trapped' in the milk compartment. This may result in the delivery of a relatively larger dose of basic drugs to the infant.

Human breast milk is an emulsion of fat in water with lactose and protein in the aqueous phase. On entering the milk compartment a drug may bind to milk protein, partition into milk lipid or remain unbound in the aqueous phase. These three variable fractions constitute the total amount of a drug contained in a given volume of milk received by the suckling infant. The dose of drug ingested by an infant is not affected significantly by milk protein because of low protein binding of drug in milk. Lipid-soluble drugs such as diazepam and phenytoin have been found to be concentrated in milk lipid [9]. The M/P ratio of a highly lipid-soluble drug may vary with changing lipid content of milk during a feed and throughout the course of lactation.

Infant pharmacokinetics

The total dose of a drug that may be delivered to a suckling infant is determined by the concentration of the drug in milk and the volume of milk consumed. Other important determinants of the infant's plasma concentration of a drug are the oral bioavailability and clearance.

Infants do not absorb and eliminate drugs in the same way as adults. In infants, higher gastric pH, different gastrointestinal flora, delayed gastric emptying time and reduced amounts of bile salts and pancreatic enzymes can influence drug absorption [10]. In premature infants the gut does not exercise selective permeability for a short period after birth and the bioavailability may approach 100% [11]. The affinity of plasma protein for drugs in neonates is also less than that of adults, leading to increased free drug concentrations. Both hepatic metabolism and renal elimination are immature in young infants, particularly premature neonates. A weak biotransformation activity, immature mechanisms for clearance and a poorly developed blood brain barrier combine to make the neonate very vulnerable to toxic effects of drugs [10,12].

Drugs in anaesthetic practice

It is often difficult to state with complete certainty whether a particular drug ingested via breast milk is known to be free of hazards to suckling infants because: (a) there is incomplete data in the literature; (b) many conclusions are drawn from a single or few case reports, or from theoretical risks; (c) many drugs have yet to be investigated fully.

It is important to emphasise that most drugs are excreted in breast milk in very small quantities. The mere presence of a drug in milk may not cause harm to the infant, unless it is present in a pharmacologically significant amount.

Table 1 shows a guide chart to drug use in breast feeding women requiring anaesthesia.

Opioids

Morphine

The British National Formulary guidelines [13] advise that, 'therapeutic doses of morphine (given to the mother) are unlikely to affect the infant'. Interestingly, the same recommendation from the American Academy of Pediatrics [14] is based on studies conducted more than 50 years ago [15] when relatively insensitive analytical methods were used. Various routes of maternal administration including the oral [16], intramuscular [17], intravenous [17], intravenous patient-controlled analgesia [18] and epidural [17,19] have all appeared to be safe for the suckling infant.

Morphine is readily absorbed from the gut and undergoes extensive first pass metabolism in adults, reducing its bioavailability to between 15 to 50% [20]. The oral bioavailability has not been studied in infants. However, in young infants, owing to immature hepatic conjugation, the elimination half-life (6.8 h) of morphine is prolonged and the clearance (6.3 $ml.min^{-1}.kg^{-1}$) reduced compared with adults, increasing the likelihood of toxic accumulation especially during chronic ingestion [21]. Robieux *et al.* [22] measured the serum morphine concentration in an infant who was breast-fed whilst the mother was receiving low doses of morphine. The infant dose reached 12% of maternal dose with the serum morphine level in the analgesic range. No adverse effects were observed in the infant despite this potentially harmful concentration of morphine. The infant was thought to have developed opioid tolerance through chronic exposure *in utero* and breast feeding.

The consequences of short-term or chronic exposure of the infant to opioids are not known but one may suspect long-term implications on the neuro-psychological development possibly through the process of 'imprinting'. Imprinting is an ethologically well documented process: a specific memory engraved during a short sensitive period leading to behavioural effects later in adult life. Jacobson *et al.* [23,24] have suggested that self-destructive behaviour (e.g. suicide and amphetamine addiction) might stem partly from an imprinting process at birth. Jacobson *et al.* [25] later provided more evidence to support the hypothesis that opiate addiction which occurred later in adult life, partly stemmed from imprinting process during birth when opiates, barbiturates or nitrous oxide were administered to the mother.

Pethidine

The quantity of pethidine excreted in breast milk is small and it would appear to be safe for suckling infants after a single maternal dose of pethidine [26]. However, pethidine and its active metabolite, norpethidine, which has a half-life of 15–20 h are both excreted in considerable amount in breast milk after patient-controlled analgesia (PCA) [18] and repeated administration [27]. Significant neurobehavioural depression was observed in the infants of nursing mothers who received pethidine by PCA compared to equivalent doses of morphine [18]. Persistently elevated norpethidine concentrations were also measured in the breast milk of these mothers. Hence, the use of pethidine in nursing mothers should probably be avoided.

Table 1. Guide chart to drug use in breast feeding women requiring anaesthesia.

	Individual drugs		
Drug groups	Indicated	Contraindicated	Comments/effects on infant
Opioids	Morphine		
		Pethidine	Neurobehavioural depression
	Codeine		
	Fentanyl		
	Sufentanil		
	Alfentanil		
Nonopioid analgesics	Paracetamol		
		Asprin	Risks of Reye's syndrome, platelet dysfunction, hypoprothrombinaemia, metabolic acidosis, kernicterus
	Ibuprofen		
	Flurbiprofen		
	Indomethacin		Monitor Convulsions reported in one infant
	Diclofenac		
	Ketorolac		Parenteral use not studied
Intravenous induction agents	Thiopentone		
	Propofol		
Inhalational agents	Halothane		Theoretically safe
	Enflurane		
	Isoflurane		
Muscle relaxants			Theoretically safe
Anticholinergics	Atropine		Possible risk of antimuscarinic effects
		Hyoscine	Possible risk of antimuscarinic effects and toxic psychosis
	Glycopyrronium		Theoretically safe
Anticholinesterases	Neostigmine		
	Pyridostigmine		
Local anaesthetics	Lignocaine		
	Bupivacaine		
		Cocaine	Cocaine intoxication reported in one infant
Benzodiazepines		Diazepam	Lethargy, weight loss, sedation
	Lorazepam		
	Midazolam		
	Temazepam		
Histamine H_2 antagonists	Cimetidine		Caution, as significant amount of drugs excreted in breast milk
	Ranitidine		
	Famotidine		
	Nizatidine		
Anti-emetics and neuroleptics		Metoclopramide	Animal studies suggest possible adverse effects on infant's nervous system
		Domperidone	
		Chlorpromazine	
		Haloperidol	
		Prochlorperazine	

Codeine

Codeine enters into milk readily, reflecting weak basic, highly lipophilic and less than 10% plasma protein binding properties. However, the highest dose of codeine ingested by the infant via milk is estimated to be much lower than the therapeutic dose. Approximately 10% of codeine is demethylated in the maternal liver to form morphine, resulting in the detection of both compounds in breast milk. Nevertheless, excretion of the metabolite, morphine, in breast milk has been found to be small and insignificant [16].

Fentanyl, sufentanil and alfentanil

Intravenous administration of 50–400 μg of fentanyl resulted in insignificant passage into breast milk [28]. This is explained by its short maternal elimination half-life of about 185 min and its rapid renal clearance [29].

Sufentanil also has a short elimination half-life of about 164 min [30]. No detectable levels of fentanyl or sufentanil were found in breast milk after single epidural doses [31].

Alfentanil is excreted in breast milk, but with the shortest terminal half-life of all opioids of about 98 min [29] and high protein-binding, was found to be safe in suckling infants [32].

Breast milk opioids and neonatal apnoea

Naumburg *et al.* [33] suggested that breast milk opioids have a causal or contributory relationship with neonatal apnoea. They reviewed one year's experience with full-term infants referred for unexplained episodes of apnoea, bradycardia and cyanosis that occurred in the first week of life and analysed their association with perinatal factors. The association with breast milk opioids proved statistically significant although neonatal plasma samples were not analysed. The opioids implicated were codeine, propoxyphene, pethidine and their metabolities which were all excreted in the milk. An infant who presented with unexplained apnoea after the study period had a low plasma concentration of morphine 108 h after the mother's last dose of morphine and at a time when no morphine was detectable in the breast milk. The authors advised that neonates with a history of apnoea, bradycardia and cyanosis should not be breast-fed by mothers taking opioid analgesics.

Nonopioid analgesics

Paracetamol

The amount of paracetamol excreted in breast milk is too small to be harmful to the infant [16,34–36], that transferred via breast milk being much lower than the lowest recommended single infant dose of 10 $mg.kg^{-1}$ [13]. However, a 2-month-old infant whose mother was receiving paracetamol developed a maculopapular rash which disappeared when the drug was discontinued and returned when paracetamol was readministered [37].

Nonsteroidal anti-inflammatory drugs (NSAIDS)

Aspirin. Aspirin is known to be excreted in breast milk [16, 38–41], and very high concentrations have been demonstrated in breast milk following a single oral dose of 650 mg [42]. Neonates may receive considerable exposure to aspirin due to immature biotransformation and excretory pathways. It is thus contraindicated in women who are breast feeding because of the possible risks of Reye's syndrome, platelet dysfunction and hypoprothrombinaemia in infants [13]. There is also a possible risk of kernicterus caused by free bilirubin which has been displaced from plasma protein by aspirin. A case of metabolic acidosis was reported in a 16-day-old suckling infant with no history of direct drug ingestion [43]. Salicylate intoxication was demonstrated as the cause based on the detection of a significant level of serum salicylate in the infant and a history of high maternal aspirin ingestion for arthritis.

Propionic acid derivatives. These are widely used for their analgesic properties and in the treatment of inflammatory disorders. Ibuprofen [44,45] and flurbiprofen [46–48] have the best documented safety in that they have been shown to be excreted in breast milk in an amount too small to be harmful to the suckling infant.

Indomethacin. Indomethacin has generally been regarded as contraindicated in breast-feeding women, ever since a single case report of convulsions in a 7-day-old infant [49]. No estimation of the drug levels was performed in the maternal serum, breast milk or infant serum. Recently, it has been demonstrated in 16 women that indomethacin was excreted in the breast milk in very small amounts. The subsequent exposure of the infants to indomethacin was extremely low as reflected in seven infants' serum levels [50]. Despite the absence of any adverse effects in the infants, the authors advised close monitoring for their possible occurrence but concluded that breast feeding need not be stopped during routine maternal indomethacin therapy.

Diclofenac. Diclofenac was not detected in breast milk after a single maternal dose of 50 mg intramuscularly or 100 mg per day orally for one week. However, the drug was measured in the breast milk of a woman who received diclofenac 150 mg daily but its excretion in breast milk was considered too small to be harmful [51–53]. Diclofenac appears to be a good choice for analgesia in nursing women.

Ketorolac tromethamine. Ketorolac tromethamine administered orally has been demonstrated to have very low concentrations in breast milk, being only 0.4% of the total daily maternal dose [54]. The investigators consider significant sequelae in the neonate unlikely but concentrations in milk after parenteral administration have not been studied.

Intravenous induction agents

Extensive literature search and inquiry from respective pharmaceutical companies yielded only a few publications which concerned thiopentone and propofol.

Thiopentone

The excretion of thiopentone in breast milk has been studied in nursing women and women undergoing Caesarean section [55]. The maximum possible amount of exposure of the infant to the thiopentone via milk following an induction dose of 3.8–7.0 $mg.kg^{-1}$ was

described as negligible. The patients undergoing Caesarean section had lower plasma and milk concentrations of thiopentone than those women who had been nursing for more than 2 weeks, possibly due to smaller doses being given and to a higher rate of metabolism in the former group. No reports of adverse effects in suckling infants have been documented.

Chronic use or therapy with other barbiturates are generally contraindicated in nursing mothers as the quantity that passes into milk is substantial [56]. Large doses in breast milk may produce drowiness and may have contributed to the death of a 13-day-old infant [57]. A single case report of methaemoglobinaemia in a suckling infant has been associated with large maternal intake of phenobarbitone and phenytoin [58]. Infantile spasms with an abnormal electroencephalogram were observed in a suckling infant after weaning from milk containing phenobarbitone [59]. Poor weight gain, a high incidence of vomiting and inadequate suckling have also been documented [60]. In the light of these reports, it may be unsafe to administer large or repeated doses, or an intravenous infusion of thiopentone to nursing mothers.

Propofol

Studies were undertaken to assess the passage of propofol into breast milk in nursing women and women undergoing Caesarean section [61,62]. Propofol was administered for induction and maintenance of anaesthesia. Analysis revealed low levels of propofol in breast milk and negligible exposure of the suckling infants through breast milk, compared to the placental transfer of the drug. Furthermore, propofol appeared to be cleared rapidly from the neonatal circulation resulting in minimal effects in the newborns [62]. These findings were consistent with, and attributed to, the pharmacokinetic profile of propofol.

Methohexitone, etomidate and ketamine

There is no information available in the literature on the excretion of these intravenous induction agents in breast milk.

Inhalational anaesthetic agents

Halothane

The excretion of halothane in breast milk was investigated in a lactating, practising anaesthetist [63]. Milk samples were obtained while she was working in the operating theatre for up to 5 h administering two different halothane concentrations (0.25% and 0.5%). Trace concentrations of halothane of approximately two parts per million in the breast milk, which were similar to those in the operating theatre environment, were found, but errors in the complex methodology might have produced an underestimate rather than an overestimate. Respiratory excretion of halothane by patients has been demonstrated to continue for up to 11–20 days after routine exposure [64], and the diffusion of halothane from blood to milk is expected to continue for a similar period. However, there have been no publications concerning the excretion of halothane in breast milk of patients who were exposed to it during general anaesthesia.

Enflurane and isoflurane

Despite the absence of information, the levels of enflurane and isoflurane excreted in breast milk of nursing mothers are expected to be negligible, at least theoretically, based on their pharmacokinetic profiles.

Neuromuscular blocking drugs

All the neuromuscular blocking drugs employed in anaesthetic practice are quaternary ammonium compounds which are fully ionized at normal body pH. They are poorly lipid soluble, do not traverse biological membranes, and are largely confined to the extracellular fluid. Hence, these drugs are not expected to cross the mammary epithelium into breast milk. They are also very poorly absorbed from the gastrointestinal tract. This fact was well known to the South American Indians, who consumed with impunity the flesh of game killed with curare-poisoned arrows. It is likely that they are safe for use in breast feeding, but we are not aware of any study which has investigated the presence of these drugs in human breast milk.

Anticholinergics

Atropine and hyoscine

Atropine sulphate and hyoscine hydrobromide are tertiary ammonium compounds which are readily absorbed from the gastro-intestinal tract and cross the blood brain barrier. Atropine is reported to appear in traces in breast milk [4,65,66] and the passage of hyoscine into breast milk has been reported to be insignificant and safe for suckling infants [13, 14, 67–69]. However, it is well recognised that infants are especially susceptible to the toxic effects of anticholinergic drugs [70]. Hyoscine, in contrast to atropine, has prominent depressant effects on the central nervous system at low therapeutic doses, probably due to its greater permeability across the blood brain barrier [66]. Toxic psychosis has also been reported to occur especially in children [71,72].

We have been unable to discover any publications concerning the specific measurement of either atropine or hyoscine concentrations in breast milk. Until clear and reliable data are available, the possible risk of antimuscarinic, central anticholinergic or toxic effects in the suckling infant remains.

Glycopyrronium

Glycopyrronium is a quaternary ammonium compound which does not cross the blood brain barrier or placenta to any significant extent. Theoretically, it is not expected to cross into breast milk in any significant amount but there is an absence of scientific data. Its absorption via the gastrointestinal tract has also been shown to be extremely poor [73].

Anticholinesterases

Neostigmine

Neostigmine, a quaternary ammonium compound with a half-life of 15–30 min, is rapidly eliminated from the

plasma when given to antagonise residual neuromuscular block [74]. Six suckling infants whose mothers were treated with high dose neostigmine for myasthenia gravis were breast-fed without side-effects, though on one occasion breast feeding was stopped as the baby appeared to have abdominal cramps after each feed [75]. Neostigmine, however, could not be detected in breast milk.

Pyridostigmine

The excretion of pyridostigmine has also been investigated [76]. The quantity in breast milk is small and together with its poor absorption from the gut, breast feeding may be regarded as safe in mothers taking these drugs.

Edrophonium and physostigmine

There is no information available on the excretion of these drugs in breast milk.

Local anaesthetic drugs

The literature contains very little information on local anaesthetic levels in breast milk.

Lignocaine

The excretion of lignocaine in breast milk was investigated in a nursing woman with mitral valve prolapse, who presented with ventricular arrhythmias [77]. She required treatment with parenteral lignocaine totalling 965 mg over 7 h. The serum and milk concentrations at the end of treatment period were 2 $\mu g.ml^{-1}$ and 0.8 $\mu g.ml^{-1}$ respectively, that is a milk concentration 40% of serum level. Plasma concentrations of lignocaine ranging from 1.19–3.10 $\mu g.ml^{-1}$ have been reported by other workers in women receiving epidural lignocaine [78–81]. Thus the possible amount of lignocaine excreted in breast milk is exceedingly small. Coupled with the additional advantage of less than 30% oral bioavailability of the drug, an infant may safely continue to breast feed from a mother on parenteral or epidural lignocaine.

Bupivacaine

The excretion of bupivacaine in breast milk was investigated in parturients receiving epidural analgesia [82]. It was not detectable in all the milk samples at the sensitivity limit of 0.02 $\mu g.ml^{-1}$. The authors concluded that epidural bupivacaine was safe for perinatal use in parturients who intended to breast feed. Data were also presented from a patient who received a bupivacaine infusion for analgesia through an interpleural catheter for 5 days whilst breast feeding without any apparent harm to her 10-month-old infant [83]. The levels of bupivacaine in breast milk were very low and bupivacaine was undectable in the infant's blood.

Prilocaine

There is no information available concerning the excretion of prilocaine in breast milk.

Cocaine

Cocaine intoxication (mydriasis, tachycardia, tachypnoea, hypertension, irritability and tremulousness) has been reported in a 2-week-old infant who ingested cocaine via her mother's breast milk [84]. Cocaine and its primary metabolite, benzoylecgonine, were demonstrated in the breast milk up to 36 h after maternal use and in the infant's urine up to 60 h after the last feed. Cocaine is highly lipid-soluble and therefore rapidly absorbed from the nose and gastrointestinal tract. Urine toxicological studies have also detected cocaine and its metabolites in adults up to 60 h after intranasal use [85]. It should thus be avoided during breast feeding.

Benzodiazepines

Diazepam

It is well recognised that transplacental transfer of diazepam may result in neonatal hypotonia, hypothermia and episodes of cyanosis and apnoea [86–89]. Diazepam and its metabolites are known to be excreted in breast milk, and lethargy, weight loss and electro-encephalographic changes characteristic of sedative medication have been reported in a breast-fed neonate whose mother was receiving diazepam 10 mg three times a day [90]. Diazepam and its long-acting metabolite, desmethyldiazepam, have been detected in the breast milk and the plasma of suckling infants by other investigators [91,92]. Although no drug effects were noticed amongst the infants, the drug levels measured might have produced such effects and, in addition, possible competition for conjugation causing hyperbilirubinaemia. These authors also cautioned the risks of drug accumulation in suckling infants and advocated that women receiving diazepam should not breast feed.

Dusci *et al.* [93], however, detected only small quantities of diazepam and its metabolites in the breast milk of a nursing mother, despite relatively large maternal intake. Only very low levels of metabolites were detected in her infant's plasma. The infant did not show any overt symptoms of intoxication. These authors concluded that the benefits of breast feeding may be acquired during maternal treatment with diazepam provided the infant's well-being is closely monitored.

Lorazepam

The amount of lorazepam detected in breast milk would result in insignificant absorption by breast-fed infants [94]. Lorazepam has also been demonstrated to be safe as an oral premedicant in nursing mothers because of its low passage into breast milk [95].

Midazolam

Midazolam and its active metabolite, hydroxymidazolam, are both excreted in small quantities in breast milk and no drug effects were observed in the infants [96]. Both substances have a short plasma half-life of 2–5 h. It is concluded that breast feeding during a short course of midazolam may be regarded as safe.

Temazepam

Temazepam is commonly prescribed as a premedicant and during the first 2 weeks postpartum. Initial limited data revealed that the amount of temazepam excreted in breast milk was small and clinically insignificant [93]. Subsequently, a more extensive investigation has confirmed that very small amounts of temazepam were excreted in breast milk and that exposure of the infants to the drug was negligible [97].

Histamine H_2 receptor antagonists

Cimetidine, ranitidine, famotidine and nizatidine have all been shown to cross into breast milk.

Cimetidine

Cimetidine concentrations were found to be considerably higher in all milk samples than the corresponding plasma samples [98]. No adverse effects on the suckling infant have been reported but the authors remained cautious regarding the use of cimetidine in nursing mothers.

Ranitidine

Ranitidine, like cimetidine, was found to transfer freely into breast milk in considerable amounts [99,100]. To date, the exposure of suckling infants to ranitidine via milk is not known to be harmful.

Famotidine

Famotidine, in comparison with the data available for cimetidine and ranitidine, is less extensively excreted in breast milk and is thus theoretically safer [101].

Nizatidine

Nizatidine is excreted into breast milk at less than 0.1% of the maternal dose [102]. Its short half-life of less than 2 h in serum and breast milk makes the risk of accumulation unlikely after multiple administration. Nizatidine thus appears to be safe in breast feeding.

Anti-emetic and neuroleptic drugs

Available data indicate that the quantity of metoclopramide [103,104] and domperidone [105,106] ingested by infants via breast milk is small, despite the former being more highly concentrated in milk than in plasma. Chlorpromazine has been detected in all breast milk samples studied (7–98 $ng.ml^{-1}$), and one infant developed drowsiness and lethargy after ingestion of milk containing 92 $ng.ml^{-1}$ of chlorpromazine [107]. The ingestion of haloperidol via breast milk by the infant, on the other hand, is regarded as small [108,109]. No data are available for droperidol, and prochlorperazine has only been shown to pass into the breast milk of lactating dogs [110].

Data on these drugs are limited. Owing to their anti-dopaminergic properties and the uncertainty regarding their effects on the infant's nervous system, it is advisable to avoid administration of these drugs to breast feeding mothers unless the clinical indications are compelling [3].

Anaesthetic management

Pre-operative considerations

Patients should be informed that all drugs administered to them may cross into breast milk, the majority in very small amounts and only those with insignificant risks to the infant would be used in anaesthesia.

The pre-operative history should include the patient's intention to continue to breast feed, medical and drug history and the infant's birth, neonatal and developmental history.

The timing of operation should be arranged to fit in with breast feeding shortly beforehand and to ensure a minimal period of starvation to avoid dehydration of the mother.

The following plan of anaesthesia may be used safely, with minimal risks to infants, in women who intend to breast feed in the postoperative period.

General anaesthesia

Premedication. Therapeutic doses of temazepam, lorazepam, midazolam, opioids and glycopyrronium may be used safely. H_2 receptor antagonists and anti-emetics (e.g. metoclopramide) should not be used routinely but only if strongly indicated.

Induction. Only thiopentone (induction doses) and propofol (induction and maintenance doses) have been shown to be safe.

Muscle relaxants and maintenance of anaesthesia. On the basis of their pharmacokinetic profiles, the use of muscle relaxants, and halothane, enflurane and isoflurane for maintenance of anaesthesia, appear to be safe despite the lack of full supporting data. Analgesia may be supplemented by using opioids or a NSAID such as diclofenac.

Postoperative analgesia. Therapeutic doses of opioids, NSAIDs such as diclofenac, ibuprofen and flurbiprofen, and regional techniques using local anaesthetics and opioids may be used. When opioids are required, it is preferable to avoid the use of pethidine. Opioids should be used cautiously or an alternative type of analgesia recommended for mothers of infants with respiratory problems as they may have increased sensitivity to breast milk opioids. Aspirin is contraindicated because of its association with Reye's syndrome in children.

Local anaesthesia

Local anaesthesia may be used solely or in combination with general anaesthesia in women who are breast feeding. Epidural bupivacaine, lignocaine, morphine, fentanyl and sufentanil may be used safely and effectively. No data are available on the use of local anaesthetics for local infiltration, peripheral nerve blocks, brachial plexus block and intravenous regional block. Apart from intercostal nerve block, all these techniques have a slower rate of systemic absorption than epidural blockade. Theoretically, at least, they are unlikely to result in any significant risks to the infants.

Conclusion

The level of information on the excretion of drugs into breast milk has improved in recent years. By understanding the principles of drug passage into breast milk and the data on specific drugs, it is possible to devise plans for anaesthesia for the mother to minimise the risks to the infant and to avoid unnecessarily depriving the infant of the benefits of breast feeding. We believe that, provided the drugs are chosen with care, elective surgery should not be postponed and breast feeding should continue in the immediate postoperative period.

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