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Review

Anaesthetic agents and excretion in breast milk

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This review is an update on anaesthetic agents and their excretion into breast milk; it presents the reported effects on suckling infants, and discusses the precautions which should be considered. For most anaesthetic agents, there is very sparse information about breast milk excretion and even less published knowledge about the possible effects on the suckling infant. Generally, when an anaesthetic agent is given on a single-dose basis, there is no evidence that it is excreted in breast milk in clinically significant amounts, even if there are detectable concentrations of the drug in the milk. Most anaesthetics are rapidly cleared from the mother, and, consequently, it should be possible to allow suckling as soon as practically feasible after surgery. However, repeated administration of certain opiates and benzodiazepines has been reported to cause adverse effects in neonates, with premature neonates apparently being more susceptible. Thus, in long-term treatment with these drugs, the importance of uninterrupted breast feeding should be assessed against possible adverse drug effects in the neonate.

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Evidence exists that breast milk has great nutritional and immunological advantages over cows' milk, and that breast feeding is the best nutritional mode for infants at least up to the age of 6 months. Consequently, it is desirable to allow breast feeding as soon as possible after anaesthesia.

With modern analytical techniques, very low drug concentrations can be measured in breast milk, and even in plasma from the suckling infant. However, there is generally a lack of information and knowledge about the practical importance of these low drug concentrations, mainly because great methodological problems arise in the assessment of drug effects and adverse effects in newborns and infants. It is often not possible to separate potential drug effects, which on the basis of the dose in milk are often presumed to be subtle and unspecific, from the infants' normal state or from concurrent disease.

Pharmacokinetic principles related to the passage of drugs are discussed in the first part of this review. In the second part, present knowledge about breast milk excretion of agents used in anaesthesiology, and the clinical implications, is summarized.

EXCRETION IN BREAST MILK

Two principal issues have an impact on the quantitative transfer of maternal drugs into milk. The first is the maternal plasma concentration, which in turn is a function of the maternal dose intake of the drug, the absorbed fraction and the total maternal clearance of the drug. The second is the influence of factors affecting the transfer of the drug from plasma to milk.

Maternal pharmacokinetics in the puerperium

In general, there is a large interindividual variability in pharmacokinetics, and many factors influence the individual capacity to metabolise drugs. During pregnancy, the metabolism and elimination of most drugs investigated are increased (1). Some agents (e.g. diazepam, nordiazepam and thiopentone) have a longer elimination half-life during pregnancy (Table 1), but this effect is apparently related to their larger volume of distribution in women at parturition rather than to a decreased clearance (2–4).

Drugs interfering with milk production

A number of drugs may directly affect milk yield. Dopamine antagonists, such as droperidol and metoclopramide inhibit the action of dopamine in the pituitary, thus enhancing prolactin secretion (5, 6) and milk production. Atropine in large doses may cause decreased lactation (7).

Translactal passage of drugs

Generally, current knowledge of the mechanisms responsible for the transfer of drugs into breast milk is fragmentary (8, 9).

As only the unbound ("free") fraction of a drug diffuses through a membrane, the degree of protein binding in plasma and milk may influence the total concentration in breast milk. In milk, drugs bind to lactalbumin, casein, and partly to other proteins such as lactoferrin (10). The protein content in breast milk varies widely. In colostrum (1–5 days), the average total protein content is 23 g/l, and in mature milk (>30 days) 9 g/l (11).

The lipid content is higher in milk than in plasma, and, consequently, drugs with great lipid solubility, including a number of anaesthetic agents, tend to concentrate in the milk. In colostrum (1–5 days), the total fat content is on the average 29 g/l, while mature milk (>30 days) contains 42 g/l (11). Thus, the amount of a drug with great lipid solubility might well be higher in mature milk than in colostrum. However, the total fat content also varies during a feed, and during the day (12).

Normally, milk has a lower pH than plasma, with variations from 6.6 to 7.0 (1). As only the non-ionised fraction of any molecule is transferred rapidly across the milk/plasma membrane, weak bases, including most anaesthetic agents, tend to have a higher milk/plasma concentration ratio than weak acids (13).

Evidence exists that there is an equilibrium between maternal blood and breast milk (9), and it has been shown that reabsorption from milk to blood does occur (10). Consequently, for practical purposes, the concentration of a drug in milk is the same regardless of whether or not some milk has previously been thrown away.

Calculation of drug dose in milk

The milk/plasma (M/P) drug concentration ratio is based on all these variables of maternal and mammary pharmacokinetics. The M/P ratio is known for some benzodiazepines and opiates used in anaesthesia (Tables 2 and 3), and is a useful parameter for calculating the total drug dose to a suckling infant. However, the M/P ratio is not constant. It may vary with regard to the milk pH, milk fat and milk protein content, and with single or multiple drug dosing (1). It may also vary with regard to the time after the dose the sampling was carried out. An M/P ratio based on samples taken before equilibrium is reached tends to be too low. Ideally, M/P ratios should be based on area under the curve (AUC) calculations, or at least multiple pairs of samples.

The average ingestion of milk by a suckling infant amounts to ca 30 ml per kg per feed and ca 150 ml per kg per 24 h (1). In the present review, these volumes are used in the calculations of the amount ingested by the infant. However, there are considerable variations. Depending on age and sex, the average 24-h milk intake may vary from 130 to 180 ml per kg. In male infants 8–13 days old, variations in milk intake from 122 to 208 ml per kg per 24 h have been observed (14).

When the mother's drug concentration in plasma and the M/P ratio are known, the daily dose to a suckling infant can be estimated as the product of the average maternal drug concentration in plasma, the M/P ratio of the drug, and the total daily milk volume ingested (1, 15). If the maximal possible exposure of a suckling infant to a drug is of interest, one should use the mother's maximal, rather than average, drug concentration in plasma, and the highest reported M/P ratio for the calculation.

DRUG DISPOSITION IN THE NEWBORN AND INFANT

The exposure of a suckling infant to a drug is not only related to the dose ingested in milk, but is also dependent on the infant's absorption, distribution, metabolism and excretion of the drug. In pre-term and full-term newborns and infants, these pharmacokinetic parameters differ markedly from the corresponding values in children and adults (Tables 1, 4–6).

Full-term neonates and infants

In newborns and infants, the gastrointestinal peristalsis is irregular, and slow gastric emptying is a major determinant of the time course of drug absorption (16).

The volume of distribution changes markedly during the neonatal period due to alterations in body composition (17) and differences in tissue and plasma protein binding (18). For several drugs, the volume of distribution per kg body weight tends to be larger in neonates than in adults, as shown e.g. for lidocaine (19) and mepivacaine (20). These factors limit the interpretation of half-life ($t_{1/2}$) values, and clearance should be the preferred method for comparing elimination capacity between children of different ages. However, most of the information in the literature is presented as half-lives.

The infant's ability to metabolise the drugs differs both qualitatively and quantitatively from that of older subjects. For example, lidocaine (19), has an extensive liver metabolism (including first-pass metabolism) in adults, but in newborns, a considerable portion of the unchanged drug is excreted in the urine (19). Thus,

the half-life of lidocaine is 2–3 times longer in neonates than in adults (Table 6). The ability to perform conjugation reactions is very inefficient at birth. Drugs such as oxazepam and morphine, which form glucuronides, have half-lives 3–4 times longer in neonates than in adults (21) (Tables 1, 4).

Pre-term neonates

Compared to full-term neonates, premature babies are more frequently delivered by caesarean section performed under general or regional anaesthesia, and they more often have diseases that may interfere with the drugs' pharmacodynamic and pharmacokinetic profile. Consequently, knowledge of the drugs that could be harmful is especially important in these cases.

The gastric emptying time and gastrointestinal absorption are even more irregular in premature than in full-term neonates. The selective permeability of the gut is underdeveloped (22), and even macromolecules may be absorbed. The protein binding of a number of drugs is decreased (23). In the liver, drug metabolism is markedly impaired and the various drug-metabolising systems mature at different rates (24,25). Glomerular filtration rate (GFR) and tubular function are also reduced to a great extent (25, 26).

INDIVIDUAL DRUGS

Diazepam

Diazepam is highly lipid soluble and un-ionised in plasma, and therefore readily crosses biological membranes. Diazepam and its main metabolite desmethyldiazepam (nordiazepam) both have long elimination half-lives, which are even longer in newborns and infants than in children and adults (2) (Table 1). The liver metabolism of diazepam is mediated via the enzyme group cytochrome P-450 II C8-10 (CYP2C8-10) (27). The enzyme activity is genetically determined, with 3–5% of Caucasians having a very low metabolic capacity. If the mother, the infant, or both, are poor metabolisers, the serum and milk levels of diazepam will be considerably higher than in fast metabolisers, with an additional risk for adverse reactions.

Table 1

Elimination half-lives of some benzodiazepines in adults and neonates. (Data pooled and derived from references 23, 35, 37, 60, 69, 70.)

Drug	Half-life, adults (h)	Half-life, neonates (h)
Diazepam	20–50[1] (65[2])	20–50[1] (400[3])
Desmethyldiazepam	50–100 (180[2])	83–138
Oxazepam	4–10	22
Midazolam	1.9	6.5 (23[3])
Lorazepam	10–18	–
Flumazenil	0.8–1.2	–

[1] Depends on the hydroxylation phenotype (see text).
[2] Highest value observed in pregnant/lactating women.
[3] Highest value observed in prematures.
– No data available.

In mothers receiving diazepam 30 mg daily for 4 to 6 days after delivery, the M/P ratio was 0.10–0.11 for diazepam and 0.08–0.13 for desmethyldiazepam (28). In plasma from the newborns, the concentration of diazepam (desmethyldiazepam) averaged 172 (243) ng/ml after 4 days (corresponding to 35% (71%) of the maternal plasma concentration), and 74 (31) ng/ml after 6 days (corresponding to 12% (6%) of the maternal plasma concentration). Despite the relatively high plasma concentrations in the neonates, no side effects were observed (28).

In later studies, the M/P-ratio varied from 0.10 to 0.58 for diazepam and from 0.08 to 0.52 for desmethyldiazepam (29–33). The majority of individual values were between 0.1 and 0.2 (Table 2). However, all these M/P ratios were calculated on the basis of single pairs of samples, and they may therefore not be as representative as ratios based on AUC values.

Taken together, these results indicate that the dose of diazepam plus desmethyldiazepam to a suckling infant will be on average 5.0% and at maximum 12% of the weight-adjusted maternal dose of diazepam (1, 30) (Table 2). Related to a therapeutic paediatric dose of 0.5 mg per kg, the suckling infant would ingest on average 1.7% and at maximum 3.8%, only.

Lethargy, weight loss and an EEG consistent with sedative medication have been reported in a 1-week-old baby whose mother had been treated with 30 mg diazepam per day for 3 days (34). The metabolite oxazepam was detected in urine from the neonate. Maternal plasma and milk levels were not determined. However, administration of diazepam to the mother before and at delivery could have contributed to the symptoms in the newborn. In a case where the mother was treated continuously with 6–10 mg per day, sedation was noted in the neonate if nursing occurred less than 8 h after taking a dose (29). In contrast to these reports, others have not observed adverse reactions (32, 33).

Taking into account the long half-lives of diazepam and its metabolites in infants, one should be aware of adverse effects (e.g. poor suckling and somnolence) if the mother receives high single doses or is treated on a long-term basis. The risk for adverse reactions is presumably greater if the infant is premature or has a very low birth-weight (35), or if the mother also has been treated with diazepam before or during delivery (1). It has been claimed that doses higher than 30 mg per day should be avoided during lactation, while

Table 2

Relative and absolute daily dose in milk of some benzodiazepines. For a full explanation, see text.

Drug (reference)	M/P-ratio[1]	Absolute dose[2] ($\mu g \cdot kg^{-1} \cdot d^{-1}$)	Relative dose[3] (%)
Diazepam (1)	0.10–0.58	3–12 (average) 7–14 (maximum)	5.0 (average in a day) 12 (maximum in a day)
Desmethyldiazepam (1)	0.08–0.52	3–9 (average) 11–13 (maximum)	–
Oxazepam (1)	0.10–0.15	4 (maximum)	0.9 (maximum in a day)
Midazolam (1, 36)	0.15	0.4[4] (maximum)[5]	0.1[4] (maximum in a feed)
Lorazepam (1)	0.22	5 (maximum)	6.1 (maximum in a day)

[1] Ratio of drug concentration in milk and maternal plasma (ranges and means).
[2] Total amount of drug ingested (μg per kg per day) by a breast-fed infant with a milk intake of 150 ml per kg per day, after average recommended daily dose to the mother.
[3] Amount of drug ingested by a breast-fed infant, in percent of the weight-adjusted maternal dose.
[4] Midazolam and α-hydroxymidazolam.
[5] Maximum in a *feed*.

doses of 10 mg or less do not produce important adverse effects in the infant (2). However, more recently, significant effects have also been noted with daily doses of 6–10 mg (29).

Midazolam

After peroral administration of 15 mg midazolam used as a hypnotic on days 2 to 6 postpartum, no detectable concentrations of midazolam or the active metabolite α-hydroxymidazolam were found in the milk 7 h after drug intake (36). At a later stage postpartum, no detectable concentrations were found later than 4 h after drug intake. The detection limits for the parent substance as well as for the metabolite were 5 nmol/l (2 ng/ml). The maximal observed concentration in milk was 9 ng/ml for midazolam and 3 ng/ml for α-hydroxymidazolam and occurred 1–2 h after drug intake. The M/P-ratio was 0.15 for both substances. No drug effects were observed in the infants (36). On the basis of these observations, the maximum ingested dose of midazolam plus α-hydroxymidazolam to the suckling infant in a feed would be 0.1% of the weight-adjusted maternal daily dose of midazolam (1) (Table 2).

Thus, the risk for the suckling infant seems to be low. Although the doses used in long-term intravenous sedation could be considerably larger than 15 mg per day, and although the elimination from neonates could be relatively prolonged (37) (Table 1), the short maternal half-life and the low passage into breast milk make it unlikely that breast feeding during a short course of midazolam treatment to the mother would be harmful for the infant.

Morphine

The first investigations into the passage of morphine into breast milk were performed in the mid 1930s (38, 39).

Table 3

Relative and absolute daily dose in milk of some opiates. For a full explanation, see text.

Drug (reference)	M/P-ratio[1]	Absolute dose[2] ($\mu g \cdot kg^{-1} \cdot d^{-1}$)	Relative dose[3] (%)
Morphine (41, 42)	2.45	15 (maximum)[5]	6 (maximum in a feed) 0.6 (average in a day) 0.9 (maximum in a day)
Pethidine (42, 43) (Meperidine)	1.07–1.20	30 (maximum)	0.5 (average in a feed) 0.7 (maximum in a feed) 2.5[4] (average in a day)
Norpethidine (42) (Normeperidine)	–	60 (maximum)	–

[1] Ratio of drug concentration in milk and maternal plasma (ranges and means).
[2] Total amount of drug ingested (μg per kg per day) by a breast-fed infant with a milk intake of 150 ml per kg per day, after average recommended daily dose to the mother.
[3] Amount of drug ingested by a breast-fed infant, in percent of the weight-adjusted maternal dose.
[4] Pethidine and norpethidine.
[5] Maximum in a *feed*.

In these studies, using insensitive and non-selective analyses with colour shift reactions (sensitivity level about 2.5 μg/ml (40)), no or only trace amounts were detected.

During recent years, interest in studying this issue has been renewed (40–42). Feilberg et al. (41) have studied the excretion of morphine in breast milk for up to 6 h after epidural, intravenous or intramuscular doses. Morphine was found to enter breast milk rapidly, and the concentration-time curves for maternal plasma and breast milk were parallel, with an M/P-ratio of 2.45. Maximum peak concentration in milk was 500 ng/ml, and appeared in one patient half an hour after administration of 10 mg morphine intravenously plus 5 mg intramuscularly. In this case, the maximal ingested dose to the infant in a meal would be 15 μg/kg, which is approximately 6% of the weight-adjusted maternal dose (Table 3). The morphine concentration in the milk fell rapidly and was below 20 ng/ml 6 h later (41). Treatment with single doses of morphine to the mother would therefore hardly be expected to cause any significant effects in a suckling infant.

Wittels et al. have compared the distribution of morphine and pethidine to breast milk (42). Five mothers received morphine intravenously, and later perorally, starting immediately after delivery. The mean cumulative maternal doses, and the morphine and morphine-3-glucuronide concentrations in breast milk are shown in Fig. 1. On the third day of life, each neonate was evaluated with the Brazleton Neonatal Behavioral Scale. On relevant subscales, neonates in the morphine group scored significantly better than neonates in the pethidine group (see also later).

A woman with systemic lupus erythematosus was treated with oral morphine 200 mg daily during the third trimester and until 1 week after delivery (40). Thereafter, morphine was gradually tapered off, and the day before the study day, she had received 40 mg. The maximal concentration in milk the next day was 100 ng/ml. The serum concentration of morphine in the neonate was 4 ng/ml, which is assumed to be in the analgesic range (40). However, no adverse symptoms were observed in the newborn.

Morphine treatment on a single-dose basis thus seems to be compatible with breast feeding, although the role of the active metabolite morphine-6-glucoronide has not been studied. Howevér, long-term treatment with morphine in high doses may cause significant plasma concentrations to be present in a suckling infant.

Pethidine

In nine lactating mothers (43), a 50-mg intramuscular dose of pethidine produced a mean peak level in breast milk of 130 ng/ml after 2 h (highest peak concentration 207 ng/ml). After 9 h, the mean level was 60 ng/ml, and after 24 h the mean concentration had decreased to 20 ng/ml. The mean M/P ratio varied between 1.07 and 1.20. The active metabolite norpethidine was not analysed. According to this study, the maximal dose to an infant in a feed would be 6.2 μg/kg, which amounts to 0.7% of the weight-adjusted maternal dose (1) (Table 3). Thus, the risk to the suckling infant seems to be negligible, and breast feeding could be assumed to be safe after a single dose of pethidine (1). However, the active metabolite norpethidine is not included in the calculation.

Wittels et al. have compared the distribution of pethidine and morphine to breast milk (42). Five

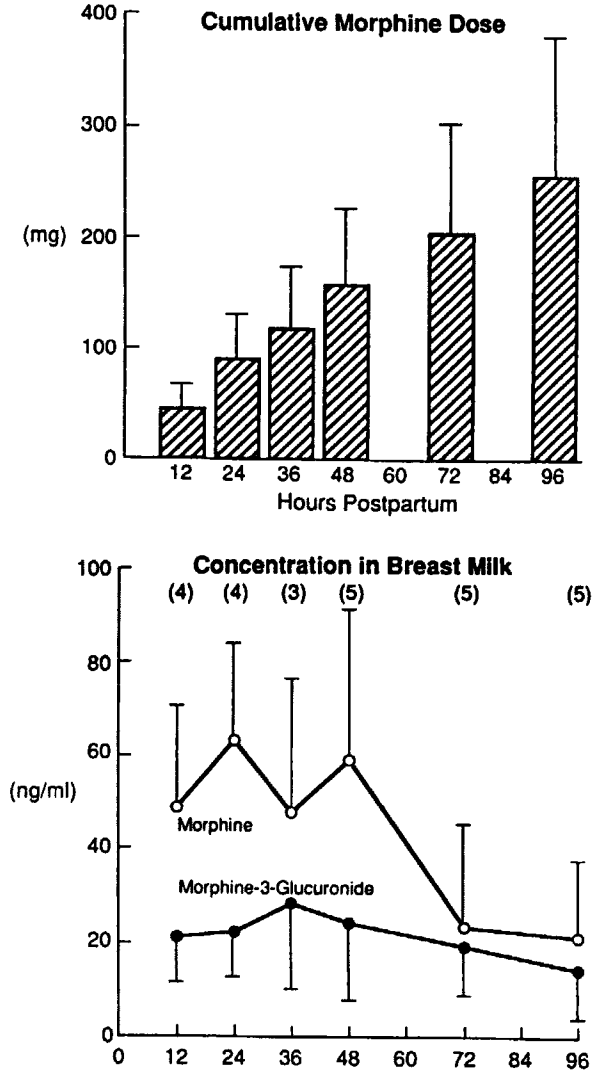

Fig. 1. Cumulative morphine doses and concentrations of morphine and morphine-3-glucuronide in breast milk from mothers receiving patient-controlled analgesia with intravenous and later oral morphine after caesarean section (mean ± s.d.). From (42), with permission.

mothers received pethidine intravenously, and later perorally, starting immediately after delivery. The mean cumulative maternal doses, and the pethidine and norpethidine concentrations in breast milk are shown in Fig. 2. The persistent elevated levels of norpethidine in breast milk, together with the long elimination half-life in newborns (23) (Table 4), may cause significant plasma levels of norpethidine in infants. This accumulation could explain the fact that neonates whose mothers were treated with pethidine had more neurobehavioral depression on the third day of life than neonates whose mothers received morphine (42).

On the basis of the significant levels in breast milk, and the long half-lives in neonates of both pethidine and norpethidine (Table 4), it has been assumed that repeated doses or long-term treatment with pethidine may produce detrimental effects in a suckling newborn (35).

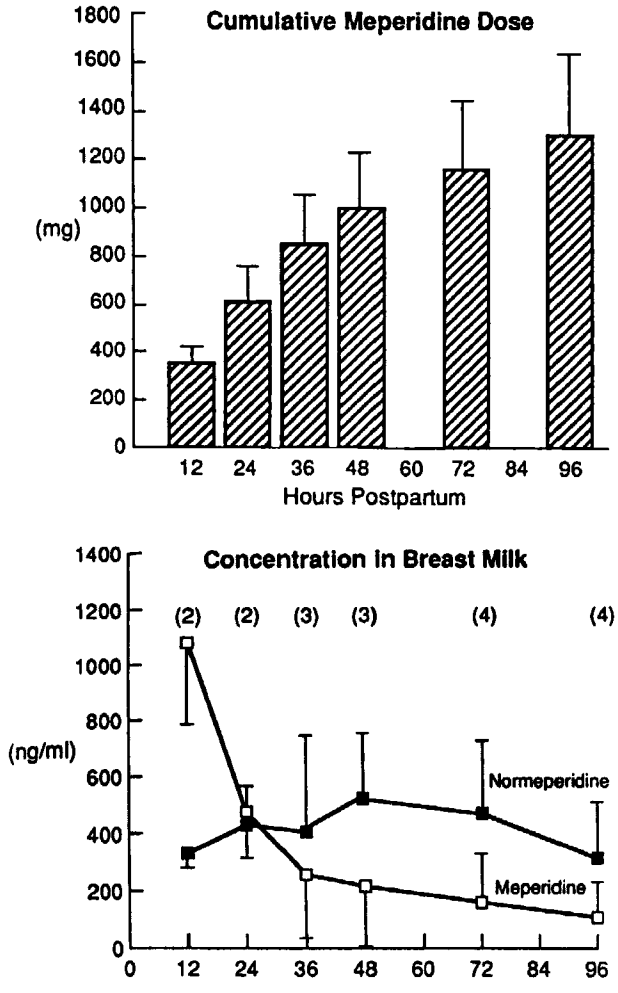

Fig. 2. Cumulative pethidine (meperidine) doses and concentrations of pethidine (meperidine) and norpethidine (normeperidine) in breast milk from mothers receiving patient-controlled analgesia with intravenous and later oral pethidine after caesarean section (mean ± s.d.). From (42), with permission.

Fentanyl

Four to seven hours after the last dose, milk was collected from ten women treated with a total of 50 to 400 μg fentanyl intravenously on request during labour (44). In most of the milk samples, the fentanyl concentrations were below the limit of detection (<0.05 ng/ml). In a few samples, the levels were between 0.05 and 0.15 ng/ml. According to these data, and assuming that the milk concentration is stable between 4 and 24 h after delivery, a suckling infant would ingest maximally 3% of the weight-adjusted maternal dose per day. On a neurobehavioral examination within the first 24 h of life, all infants had normal scores (44).

The low concentrations in breast milk are consistent with the short elimination half-life in adults (Table 4). Although fentanyl is sometimes cleared very slowly from neonates (45), the small dose in milk will hardly cause any adverse effects in the infant. Thus, breast feeding may presumably be regarded as safe after the administration of single doses to the mother.

Other opiates

For alfentanil and sufentanil, no published data on excretion in breast milk are available. However, both substances are rapidly cleared from the mother (Table 4), and although the half-lives in neonates are longer (46–48), it is unlikely that there will be substantial effects on the suckling infant after short-term exposure to the mother.

Barbiturates

Andersen et al. gave thiopentone in a mean dose of 5 mg per kg body weight to eight women who underwent caesarean section and to eight lactating women who underwent surgery more than 2 weeks after labour (49). The exposure to the neonate through breast

Table 4

Elimination half-lives of some opiates in adults and neonates. (Data pooled and derived from references 35, 45, 46, 47, 48, 60, 69, 70).

Drug	Half-life, adults (h)	Half-life, neonates (h)
Morphine	2–3	13.9
Pethidine (Meperidine)	2–4	6–32 (63[1])
Norpethidine (Normeperidine)	14–21	20–36
Fentanyl	3–4	3–13[2]
Alfentanil	1.5–2	5–6 (10[1])
Sufentanil	2–3	13 (19[1])

[1] Highest value observed in prematures.

[2] May be even longer in individual neonates (45).

milk was negligible compared to the placental transfer of the drug when used in caesarean section. The maximal thiopentone concentrations were 0.34 μg/ml in colostrum and 0.9 μg/ml in mature milk, at the first sampling time after 4 and 2 h, respectively. The M/P ratio was 0.4–0.5 for both colostrum and mature milk. Consequently, the maximal daily dose to the infant is estimated to be 0.135 mg/kg, which is approximately 3% of an adult intravenous induction dose. Although the half-life in neonates could be long (Table 5), this dose may be regarded as negligible.

Inhalational anaesthetics

Coté et al. (50) have detected trace concentrations of halothane in breast milk from a lactating, practising anaesthesist. After 5 h in the operating theatre, the halothane concentration in milk was 2 ppm. At another exposure 1 week later, the concentrations were 1.9 ppm and 0.83 ppm in milk, and 1.54 ppm and 0.27 ppm in air after 1.5 and 4 h, respectively. Halothane concentrations in breast milk may vary considerably with the fat content (50). Although the levels in breast milk would be higher when pharmacologically active amounts are given to the mother, the dose to the infant is assessed as negligible at the time when lactation is practically feasible after surgery.

For isoflurane, enflurane, sevoflurane and desflurane, no information is available, but the risk for the suckling infant has been considered to be very low also for these agents (35).

Neuroleptics

There is no published information on the excretion of droperidol into breast milk, but based on chemically related agents, some assumptions can be made.

The elimination half-life of droperidol is 1.5–2 h in adults (51) (Table 5). For the chemically closely related butyrophenone haloperidol, which in addition has a considerably longer half-life, the quantity of drug ingested by a suckling infant is as small as 0.2–2.1% of the weight-adjusted maternal daily dose (1). Thus, even though data are missing, the potential for any pharmacological effect in the suckling infant is by analogy considered to be very low when droperidol is given on a single-dose basis.

From long-term treatment in rats, there is some evidence that exposure to neuroleptics through milk alters dopamine receptor sensitivity. These changes correlate with disturbances in motor development and learning behaviour (52). The interpretation of these animal data is complicated because the rat nervous system is at an earlier stage of development than the human brain during the first postnatal weeks (53), and the significance remains to be established.

Table 5

Elimination half-lives of some intravenous anaesthetics in adults and neonates. (Data pooled and derived from references 23, 60, 69.)

Drug	Half-life, adults (h)	Half-life, neonates (h)
Thiopentone	8–11 (26[1])	20
Methohexital	2–6	–
Ketamine	2–3	–
Droperidol	1.5–2	–
Propofol	4–7[2]	–
Etomidate	3–6	–

[1] Highest value observed in pregnant/lactating women.

[2] Propofol may have a very slow terminal elimination phase; maximum estimated half-life in this phase is 63 h (57).

– No data available.

Propofol

In 21 women who underwent elective caesarean section, anaesthesia was induced with an intravenous bolus of 2.5 mg propofol per kg body weight (54). In 11 of these, a continuous infusion of 5 mg/kg per hour was started after the induction dose. Propofol concentrations in milk from the subjects treated solely with the bolus dose were 0.14–0.24 μg/ml after 4 h and 0.089–0.19 μg/ml after 8 h. In milk from one mother in the other group, the propofol concentration was 0.74 μg/ml after 5 h and 0.048 μg/ml after 24 h. The exposure through breast milk was thus negligible compared to the placental transfer of the drug when used in caesarean section (54).

After an induction dose of 2.5 mg propofol per kg body weight, and maintenance with propofol for up to 30 min, Schmitt et al. (55) found propofol concentrations of 0.12–0.97 μg/ml in colostrum 4–8 h later. The M/P ratio varied from 0.6 to 1.3. According to this, the maximal dose to the infant in a feed would be 1.5% of the weight-adjusted maternal dose, and below 0.1% of the weight-adjusted mean dose used for long-term sedation in a 4-week old girl (56).

Although propofol is a short-acting agent, evidence exists that it has a very slow terminal elimination in adults (maximal half-life 63 h), representing redistribution from deep compartments (57). However, used for induction or in short-term infusion to the mother, the amount representing this terminal phase is small. Therefore, although propofol may be harmful when used for long-term sedation in infants (56), there is no evidence that propofol would cause detrimental effects in a suckling infant when given to the mother in a single dose or on a short-term basis.

Muscle relaxants and reversing agents

No published information is available on the transfer of muscle relaxants into breast milk. However, based

on the pharmacokinetic properties of the agents, some assumptions can be proposed.

Succinylcholine (suxamethone) administered intravenously is hydrolysed up to 80% before reaching the neuromuscular junction (58), and further inactivated by plasma cholinesterase (pseudocholinesterase) with an elimination half-life of approximately 3–5 min (58). For practical purposes, one should assume that the whole drug amount is cleared from the mother in less than half an hour. Thus, succinylcholine is rapidly metabolised in plasma, and it is very unlikely that the drug is excreted in milk in significant amounts.

The elimination half-life for pancuronium is 1.5–3 h and for vecuronium 1–2 h (59). Atracurium undergoes a fast and spontaneous degradation in plasma with an elimination half-life of approximately 20 min (59). The metabolites have no or very little neuromuscular blocking activity (59).

At physiological pH, succinylcholine, pancuronium and atracurium are bisquaternary ammonium compounds; vecuronium is a monoquaternary compound (59). Generally, ionised drugs pass slowly through biological membranes. Even if trace amounts should be excreted into breast milk, quaternary ammonium muscle relaxants are poorly absorbed from the gastrointestinal tract (60).

Neostigmine is a quaternary ammonium compound at physiological pH, and has been thought not to be excreted in breast milk (61). However, with modern analytical techniques, the closely related quaternary ammonium compound pyridostigmine is found in breast milk (62). The M/P ratio for pyridostigmine is 0.3–0.6. Thus, the infant would ingest on average 0.08% of the weight-adjusted maternal daily dose of pyridostigmine (1). The American Academy of Pediatrics considers pyridostigmine to be safe in breastfeeding (63).

Local anaesthetics

In a case report, a lactating woman treated with intravenous lidocaine for ventricular dysrhythmias was presented (64). The M/P ratio was 0.4. Thus, if a mother receives a dose of lidocaine leading to a plasma concentration at the upper limit in the usually recommended antiarrhythmic interval, i.e. 6 μg/ml (64), the concentration in breast milk would amount to 2.4 μg/ml. In such a case, the oral intake of lidocaine in a suckling infant would amount to 360 μg/kg per day, which is 0.8% of the recommended antiarrhythmic daily dose given by infusion to infants. The peroral bioavailability of lidocaine is poor, but the first-pass metabolism appears to be less in newborns than in adults (19). However, even with maximal antiarrhythmic maternal doses, the lidocaine content in breast milk is so low that the differences in the metabolic capacity of the infant have no practical interest. When lidocaine is used as an anaesthetic maternal doses and, consequently, the amounts in breast milk are even smaller. The half-life is short in both adults and neonates (Table 6). Lidocaine should therefore be considered to be safe in breastfeeding (56, 64).

Table 6
Elimination half-lives of local anaesthetics in adults and neonates (23).

Drug	Half-life, adults (h)	Half-life, neonates (h)
Lidocaine	1.0–2.2	2.9–3.3
Bupivacaine	1.2–4.6 (9.0[1])	6.0–22.0
Mepivacaine	1.7–6.9	5.3–11.3

[1] Highest value observed in pregnant/lactating women.

Following bupivacaine epidural anaesthesia for vaginal delivery, no detectable concentrations in breast milk were found (65). The limit of detection was 0.02 μg/ml, and samples were taken 2, 8, 24, and 48 h after delivery.

Baker & Schroeder (66) gave interpleural bupivacaine to a lactating woman for postoperative pain relief after cholecystectomy. After a bolus dose of 50 mg, she was treated with a continuous infusion of 25 mg per hour for 5 days. Six hours after the bolus dose, the bupivacaine concentration in breast milk was 0.45 μg/ml, and, later, the concentration varied between 0.1 and 0.3 μg/ml. In serum from the infant, there were no detectable amounts of bupivacaine (limit of detection not mentioned, but apparently less than 0.1 μg/ml) in a sample taken on the 3rd day. No unusual infant behaviour was noted. On the basis of these reports (65, 66), bupivacaine should be considered as safe.

Anticholinergics

The available knowledge on anticholinergics and excretion into breast milk is very limited. Whether or not atropine is excreted in breast milk in significant amounts is controversial (67), and neither the excretion in breast milk nor a possible anticholinergic effect in the infant has been adequately documented. Although neonates are thought to be particularly sensitive to anticholinergic effects and although anticholinergic effects have been suspected in suckling infants (7, 14, 68), the American Academy of Pediatrics considers atropine and scopolamine to be compatible with breast-feeding (63).

CONCLUSION

To date, there is no evidence that any anaesthetic agent used on a single-dose basis to the mother causes

detrimental effects in healthy suckling newborns and infants. Anaesthetics are rapidly cleared from the mother, and although they generally have longer half-lives in neonates than in adults, the importance of this factor is limited after administration of a single dose to the mother. Based on the present literature, our assessment is that lactation could be allowed as soon as practically feasible after surgery, without throwing away portions of the milk.

The risk of adverse effects in the suckling infant increases with repeated administration, as clearly shown for diazepam and pethidine. Premature neonates, or newborns with concurrent disease or low birth weight, are presumably more susceptible to such adverse reactions. Thus, it could be pertinent to avoid breast feeding when lactating mothers receive long-term treatment with benzodiazepines or opiates, especially if these drugs are given in high doses or in combination therapy, or if the newborn is premature, has low birth weight or concurrent disease. However, in all long-term treatment cases, an individual risk/benefit analysis should be performed.

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