REVIEW ARTICLE

Paediatr Drugs 2000 May-Jun; 2 (3): 223-238
1174-5878/00/0005-0223/$20.00/0

Analgesics and Breast-Feeding
Safety Considerations

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Abstract

The issue of prescription of analgesics during lactation is clinically important but also complex. Most of the information available is based on single dose or short term studies, and for many drugs only a single or a few case reports have been published. As great methodological problems exist in the assessment of possible adverse drug reactions in neonates and infants, there is limited knowledge about the practical impact of the, often very low, concentrations found. Nevertheless, some recommendations can be made.

Breast-feeding during maternal treatment with paracetamol (acetaminophen) should be regarded as being safe. Short term use of nonsteroidal anti-inflammatory drugs seems to be compatible with breast-feeding. For long term treatment, short-acting agents without active metabolites, such as ibuprofen, should possibly be preferred. The use of aspirin (acetylsalicylic acid) in single doses should not pose any significant risks to the suckling infant.

Use of codeine is probably compatible with breast-feeding, although the effects of long term exposure have not been fully elucidated. For propoxyphene, it seems unlikely that the suckling infant will ingest amounts that will cause any detrimental effects during short term treatment. However, it cannot be excluded that significant amounts of the metabolite norpropoxyphene may arise in the suckling infant during long term exposure.

Treatment of the mother with single doses of morphine or pethidine (meperidine) is not expected to cause any risk for the suckling infant. Repeated administration of pethidine, in contrast to morphine, affects the suckling infant negatively. Thus, morphine should be preferred in lactating mothers. However, during long term treatment with morphine, the importance of uninterrupted breast-feeding should be assessed on an individual basis against the potential risk of adverse drug effects in the infant. If it is decided to continue breast-feeding the infant should be observed for possible adverse effects.

In general, if treatment of a lactating mother with an analgesic drug is considered necessary, the lowest effective maternal dose should be given. Moreover, infant exposure can be further reduced if breast-feeding is avoided at times of peak drug concentration in milk. As breast milk has considerable nutritional, immunological and other advantages over formula milk, the possible risks to the infant should always, and on an individual basis, be carefully weighed against the benefits of continuing breast-feeding.

Breast-feeding is superior to formula feeding in many ways. Breast milk has nutritional advantages over formula milk, and contains enzymes that promote digestion and absorption of nutrients. Breast milk gives better protection against infectious diseases such as diarrhoea, otitis media and respiratory and urinary tract infections.[1-4] Breast-feeding has also been linked to a lower prevalence of atopic eczema and food allergy[5] and to an enhanced antibody response to vaccination.[6] Moreover, breast-feeding has the advantages of simplicity and portability and is less expensive than formula feeding, both in terms of direct costs and healthcare costs.[7,8] For the nursing mother, suckling promotes postnatal uterine involution, and a long duration of breast feeding is thought to protect against breast cancer.[9] Last but not least, breast-feeding is an important opportunity to enhance the quality of the mother-child interaction. Taking into account these advantages, it is essential that possible risks to the infant during maternal drug treatment are carefully weighed against the benefits of continuing breast-feeding, as the infant should not unnecessarily be denied breast-feeding. In this risk-benefit analysis, knowledge about the excretion of drugs into breast milk is of vital importance.

It is a concern that much of the information on the excretion of analgesics into breast milk is based on single dose or short term studies, and for many drugs on only one or a few case reports. Moreover, although very low drug concentrations can be measured in breast milk with modern analytical techniques, there is generally a lack of knowledge about the practical importance of these low doses reaching the infant. Another concern is the great problems involved in the assessment of possible adverse drug reactions in neonates and infants. Given these methodological limitations, it is not surpris-

ing that conclusive data and, thereby, unambiguous recommendations are lacking for many drugs.

Pharmacokinetic principles related to the passage of analgesics into breast milk are presented in the first part of this review. In the second part, present knowledge about the excretion of specific analgesics in breast milk is summarised and its clinical implications are discussed.

1. Methods

Medline and EMBASE searches using the terms 'milk', 'human', 'breast-feeding' and 'lactation' were carried out for all substances included in this review. Moreover, previously published review articles and textbooks, as well as the original research articles provided by the database searches, were scrutinised in order to identify supplemental publications. Drugs used as adjuvant analgesics such as antidepressants and anticonvulsants are not included in the present review; the excretion of these drugs into breast milk has, however, recently been extensively reviewed elsewhere.[10]

2. Principles of Drug Excretion Into Breast Milk

2.1 Maternal Pharmacokinetics

The most important factor accounting for the considerable interindividual pharmacokinetic variability is the genetically determined oxidative liver enzyme capacity. Many analgesics, including most nonsteroidal anti-inflammatory drugs (NSAIDs), are metabolised by the hepatic cytochrome P450 (CYP) enzymes CYP2C9 or CYP2D6 (table I).[11,12] The activities of these enzymes are bimodally distributed in the population and an individual can thus be classed as either an extensive metaboliser (EM) or a poor metaboliser (PM) for each of these enzyme activities. The prevalence of CYP2C9 PMs is less than 1%,[11] whereas the prevalence of CYP2D6 PMs varies from 1 to 7% according to race.[13] If the mother, the infant, or both, are CYP2C9 PMs and a standard maternal NSAID dose is given, infant plasma concentrations of the drug will most probably be higher than average,[11] with an assumed increased risk of adverse drug reactions. In contrast, the risk of adverse effects during treatment with codeine might possibly be lower in CYP2D6 PMs, as codeine is bioactivated to morphine by this enzyme.[12]

Table I. Analgesic drug substrates of the polymorphic cytochrome P-450 (CYP) enzymes CYP2C9 and CYP2D6[11,12]

CYP2C9	CYP2D6
Diclofenac	Codeine
Flurbiprofen	
Ibuprofen	
Mefenamic acid	
Naproxen	
Piroxicam	
Tenoxicam	

2.2 Translactal Passage of Drugs

As only the unbound (free) fraction of a drug diffuses through biological membranes, the degree of protein and lipid binding in plasma and breast milk influence the total drug concentration in breast milk. For example, as most NSAIDs are, to a high degree, bound to plasma proteins, the excretion in milk is relatively low. As the triglyceride content is higher in breast milk than in plasma, drugs with a high lipid solubility, such as the opioid analgesics, tend to concentrate in milk. Moreover, the triglyceride content is higher in mature milk than in colostrum and higher in postfeed milk than in prefeed milk. Consequently, the concentration of lipid-soluble drugs will generally be higher in mature milk than in colostrum and higher in postfeed milk than in prefeed milk.[14,15] In addition, the total lipid content also varies considerably between feeds and between individuals.[16]

Milk has a lower pH than plasma, with variations from 6.6 to 7.0.[17] As only the non-ionised fraction of any molecule is transferred rapidly across the milk/plasma (M/P) membrane, milk concentrations of weak acids, such as the NSAIDs, tend to be lower than the concentrations of weak bases.

3. Calculation of Drug Dose to the Infant

The M/P drug concentration ratio is a frequently used quantitative measure of the translactal passage of a drug. The M/P ratio for a given drug may, however, vary with regard to milk pH, milk triglyceride and milk protein content, and with single or multiple drug administration.[17] Moreover, it may vary with the time interval between drug intake and sampling time, as the milk concentration-time curve usually lags behind the plasma concentration-time curve.[18] Ideally, M/P ratios should therefore be based on area under the curve (AUC) calculations or at least on multiple pairs of samples, obtained at equilibrium of distribution.

When estimating the drug exposure to the infant, the milk volume ingested by the infant is most often assumed to be 150 ml/kg/24 hours.[17] This volume is also used in the calculations in the present review. However, it is well known that there are considerable variations in milk intake between infants. For example, in 8- to 13-day-old male infants, variations in milk intake from 122 to 208 ml/kg/24 hours have been observed.[19] For drugs with short half-lives, such as most analgesics, it can be more relevant to compare doses ingested in a feed. For such calculations it is assumed that the average milk volume intake amounts to 30 ml/kg bodyweight.[17]

When the maternal plasma drug concentration and the M/P ratio are known, the daily dose to a suckling infant can be estimated as the product of the maternal drug concentration in plasma, the M/P ratio of the drug and the total daily milk volume ingested. The estimated relative daily dose to the suckling infant can then be expressed per kg bodyweight as a percentage of the maternal dose per kg bodyweight.

The presence of active metabolites should be considered when evaluating the possible risk of pharmacological effects in the infant and should also be included in the calculations of infant dose. In addition, the content of active and inactive glucuronides, such as paracetamol glucuronide, piroxicam glucuronide and the morphine glucuronides, should be taken into account.[20]

4. Principles of Drug Disposition in the Infant

Drug exposure to a suckling infant is not only related to the dose ingested but is also dependent on the infant's absorption, distribution, metabolism and excretion of the drug.[21,22] In pre-term and full term neonates and infants, these parameters may differ markedly from the corresponding values in children and adults. Infant age is therefore a critical factor to take into account in the individual risk analysis. Although there is generally a lack of studies on the elimination of analgesics in neonates and infants, data are available for a few drugs (table II).[23-29]

4.1 Hepatic Biotransformation

The various drug-metabolising enzymes in the liver seem to mature at different rates.[21,22] For the most important enzymes, the metabolic activity seems to approach that in adults approximately 2 to 3 months postnatally. Thereafter, the metabolic rate continues to gradually increase up to an order of magnitude 2 to 6 times that in adults. If the infant is a poor metaboliser with respect to the enzymes CYP2C9 or CYP2D6 (see section 2.1), the infant will, independent of age, have a low capacity to

Table II. Elimination half-lives of some analgesics in adults and neonates[23-29]

Drug	Elimination half-life (h)	
	adults	neonates
Non-opioid analgesics		
Paracetamol (acetaminophen)	2.5	2.8
Salicylate	2-3[a]	5-12[a]
Indomethacin	2-11	14-20
Opioid analgesics		
Morphine	2-3	3-14
Pethidine (meperidine)	2-4	6-32 (63[b])
Norpethidine (normeperidine)	14-21	20-36
Fentanyl	3-4	3-13[c]

a Salicylate displays nonlinear (dose-dependent) kinetics. The values given are the half-lives at low concentrations when the elimination is linear. At high concentrations the half-life may increase to ≥30 hours.

b Highest value observed in premature infants.

c May be even longer in individual neonates.[23]

Table III. Milk/plasma concentration ratios and relative doses to the suckling infant for paracetamol (acetaminophen) and phenacetin

Drug	Number of cases	Milk/plasma concentration ratio	Relative dose to the suckling infant (%)[a]		Reference
			maximum in a feed	maximum in a day	
Paracetamol	13	0.95 ± 0.16[b,c]	1.9		32
		1.24 ± 0.12[b,d]			
Paracetamol	3	0.76 ± 0.04[b]	2.1	1.5	33
Paracetamol	12	0.7-1.1	4.8		34
Paracetamol	1	0.50-0.74	1.3		35
Phenacetin	2	0.39-0.67 (PHE)	0.65 (PHE)	0.12 (PHE)	36
		0.81-1.42 (PAR)	0.98 (PHE + PAR)	1.5 (PHE + PAR)	

a Infant dose per kg bodyweight as a percentage of maternal dose per kg bodyweight.

b Mean ± SD.

c In colostrum.

d In mature milk.

PAR = paracetamol (acetaminophen) [metabolite from phenacetin]; **PHE** = phenacetin.

metabolise drugs for which these enzymes are of importance (table I).

In neonates, the ability to perform most conjugation reactions is impaired to an even greater extent than the oxidative metabolic capacity.[22,30] Drugs that form glucuronides without any major alternative metabolic pathway, such as morphine, have half-lives 3 to 4 times longer in neonates than in adults (table II).[21] On the other hand, a full term neonate seems to be able to handle oxazepam efficiently, probably by glucuronide conjugation, less than 1 week postnatally.[31] One explanation might be that several isoenzymes that mature at different rates are involved in the conjugation reactions to glucuronide.

Some data indicate that the sulphate conjugation pathway is fully developed already at approximately 30 weeks of gestation age. Although the major metabolic pathway of paracetamol (acetaminophen) in adults is glucuronide conjugation, sulphate conjugation is an important pathway in neonates. Paracetamol can therefore be efficiently handled independently of age, as illustrated by the fact that the paracetamol has approximately the same half-life in neonates as in adults (table II).[28]

4.2 Renal Excretion

Between 28 and 34 weeks of gestational age the glomerular filtration rate is approximately 25% of that in adults. Thereafter, it gradually increases until adult values are reached by 2.5 to 5 months of age.[22,30] Tubular function is even more impaired in neonates and reduced tubular function may persist up to 6 to 9 months of age.[22,30] The capacity for renal excretion is of minor importance for the elimination of analgesics, with the exception of the excretion of glucuronide and sulphate conjugates, which is generally reduced in individuals with impaired renal function, including neonates.

5. Excretion of Non-Opioid Analgesics in Breast Milk

5.1 Paracetamol (Acetaminophen)

M/P ratios for paracetamol have most often been reported to be between 0.7 and 1.3. The maximum dose in a feed can, in most cases, be estimated to be less than 5% of the bodyweight-adjusted maternal dose (table III). Consequently, if the mother takes the maximum recommended daily dose of 4g, the infant will, as an absolute maximum, receive a dose of 2.8 mg/kg bodyweight, or approximately 5% of a therapeutic infant dosage of 60 mg/kg/day. In most cases infant exposure will be considerably lower.

In 2 studies, it was reported that no drug effects were observed in the infants.[34,37] On the other hand, in a case report a 2-month-old infant whose mother received paracetamol developed a rash which dis-

appeared when the drug was discontinued and reappeared when paracetamol was reinstituted.[35]

As neonates are able to metabolise paracetamol as efficiently as adults (table II) and as no dose-dependent adverse drug reactions have been described in infants, breast-feeding should be considered to be compatible with maternal treatment with paracetamol.

5.2 Aspirin (Acetylsalicylic Acid)

Excretion of salicylic acid into breast milk has been known at least since 1935.[38] Most of the reported M/P ratios are within the range 0.03 to 0.2 (table IV), and the maximum dose in a feed is estimated to be 8.1% of the bodyweight-adjusted maternal dose. The total exposure can, however, be higher since the metabolite salicylate glucuronide has not been taken into account.[20,44] Moreover, because of the nonlinear kinetics of salicylate, larger amounts than reported in the single dose studies could be present during long term treatment with higher doses. In addition, the elimination half-life in neonates is considerably longer than in adults (table II).

Aspirin taken in late pregnancy can cause renal dysfunction and haemostatic abnormalities in the fetus and the neonate.[45] Moreover, use of aspirin in children has been associated with Reye's syndrome. It is not known whether these factors have relevance when the infant is exposed through milk. A 16-day-old infant whose mother received a daily dose of aspirin 3.9g developed metabolic acidosis and had a serum salicylate concentration of 240 mg/L.[46] In a few other infants, plasma salicylate concentrations have been quantified (table V). Thrombocytopenic purpura has been reported in an infant who was exposed to salicylate via breast milk.[48] On the other hand, in a prospective study of possible adverse effects in breast-fed infants of 15 mothers who ingested aspirin, no negative effects were observed.[37] In fact, possible beneficial effects in infants have also been described. In a non-blind trial, 18 of 22 breast-feeding mothers reported a definite improvement in the infants' colic symptoms after starting aspirin therapy.[49]

There is no clear consensus regarding the use of aspirin in lactating mothers. According to the American Academy of Pediatrics, aspirin should be used with caution because of the possible risk of adverse effects in the suckling infant.[50] Others regard aspirin as not suitable for use during lactation,[51] at least when administered long term,[17] when administered in daily doses of more than 2.4g,[52] or when the infant is less than 2 months of age.[53] Thus, if high doses have to be used for a longer period of time, stopping breast-feeding should be considered. When using lower doses for long term treatment the infant should be observed for possible adverse effects. Intermittent use should not pose a risk to the infant. In order to decrease the potential risks further, the mother could preferably avoid breast-feeding during the first hours after aspirin intake.[54]

5.3 Diclofenac

M/P ratios and relative doses to the infant for diclofenac and other NSAIDs are summarised in table VI.

Table IV. Milk/plasma concentration ratios and relative doses to the suckling infant for salicylate after maternal intake of aspirin (acetylsalicylic acid)

Drug	Number of cases	Milk/plasma concentration ratio	Relative dose to the suckling infant (%)[a]		Reference
			maximum in a feed	maximum in a day	
Aspirin	1	0.04-0.08	2.6		39
Aspirin	1	<0.3			40
Aspirin[b]	2	0.03-0.05	0.3		36
Aspirin[b]	6		8.1		41
Aspirin[b]	8	0.024-0.14	0.5	2.5	42, 43

a Infant dose per kg bodyweight as a percentage of maternal dose per kg bodyweight.

b Not studied during steady state conditions.

Table V. Concentrations of salicylate in serum from suckling infants after maternal ingestion of aspirin (acetylsalicylic acid). These are all reports of single cases

Maternal dosage (mg/day)	Infant age	Infant plasma concentration (mg/L)	Reference
4000	Several weeks	<50	40
3900	16 days	240[a]	46
2400	9 weeks	65	47

a Adverse effects reported (see section 5.2).

According to unpublished data referred to in a review article,[56] diclofenac was not detected in breast milk of mothers who received 100 mg/day (the limit of detection and the number of participants was not reported). A woman who was treated with diclofenac 150 mg/day had a milk concentration of 100 μg/L. As diclofenac has a short elimination half-life (1 to 2 hours in adults) and no active metabolites, and as the amount excreted in milk is very small, the drug is most often regarded to be compatible with breast-feeding.[44,51,77]

5.4 Ibuprofen

Ibuprofen has an elimination half-life of approximately 2 hours in adults and is metabolised to inactive products. The M/P ratios reported are very low (table VI).[63-65]

In one study, ibuprofen was measured in maternal serum and milk in 12 mothers who received 400mg every 6 hours for pain relief after caesarean section.[63] At steady-state conditions the concentrations were below the limit of detection (<1.0 mg/L) in all milk samples. In another study, a lactating mother was treated for 3 weeks with ibuprofen 400mg twice daily and ibuprofen concentrations in maternal serum and milk were followed for 3.7 and 8 hours after administration, respectively.[64] The maximum concentration in serum was 18.2 mg/L, but the concentrations were below the limit of detection (<0.5 mg/L) in all milk samples.

In yet another study, 10 breast milk samples were obtained from a lactating mother who had received ibuprofen after maxillary surgery.[65] Over a period of 40 hours, 6 tablets of 400mg were administered. The highest ibuprofen concentration in milk was 0.18 mg/L. Moreover, in a study of 21 suckling infants, no adverse effects were observed.[37] Based on the low excretion into milk, the short half-life of the drug and the absence of reported adverse effects in the infants, breast-feeding during maternal ibuprofen treatment should be regarded as being safe.

5.5 Indomethacin

Indomethacin has an elimination half-life of 4 to 5 hours in adults. M/P ratios and relative doses to the suckling infant for indomethacin are presented in table VI. In a study of 16 nursing mothers taking 75 to 300 mg/day orally or rectally,[66] 1 of the 7 infants studied had plasma concentrations above the limit of detection (table VII). No drug-related adverse effects were seen in these 7 infants. In contrast, neonatal convulsions were observed in a 1-week-old baby whose mother had been treated with indomethacin 200 mg/day for 3 days.[79] Plasma and milk concentrations were not determined but indomethacin was detected in the urine from the neonate. It has, however, been questioned whether there was a causal link between the treatment and the convulsions.[80] No data exist on infant exposure after long term maternal treatment.

In conclusion, the exposure of the suckling infant to indomethacin seems to be low. The American Academy of Pediatrics considers the drug to be compatible with breast-feeding.[50] On the other hand, others have recommended that its use should be avoided in lactating mothers on the basis of the reported case of seizures.[79]

5.6 Naproxen

According to unpublished data referred to in a review article, the M/P ratios for naproxen have been reported to be low (table VI).[71] In a woman who received naproxen 250 to 375mg twice daily on a long term basis,[70] the highest milk concentration was 2.4 mg/L and appeared 4 hours after administration. The relative dose to the infant can be estimated to be 2.8% (table VI) and naproxen was found to be excreted in the urine of the infant.

Table VI. Milk/plasma concentration ratios and relative doses to the suckling infant for nonsteroidal anti-inflammatory drugs

Drug	Number of cases	Milk/plasma concentration ratio	Relative dose to the suckling infant (%)[a]		Reference
			maximum in a feed	maximum in a day	
Azapropazone	4			4.1[b]	55
Diclofenac	NR			0.7	56
Dipyrone[c]	8	0.97-1.84 (MAA)	3.7 (MAA)		57
		0.60-1.52 (AA)	2.8 (AA)		
		0.94-1.25 (FAA)	0.5 (FAA)		
		0.77-1.50 (AAA)	1.3 (AAA)		
Etofenamic acid[c]	3			0.0 (EFA) 0.4 (FFA)	58
Fenbufen	9	<0.01[d]			59
Flufenamic acid	10	0.008-0.019[e]	0.4	0.6	60
Flurbiprofen	12	0.008-0.027[f]	0.3	0.3	61
Flurbiprofen[c]	10	0.013-0.028	0.2	1	62
Ibuprofen	12	<0.06[d]	<0.5[d]		63
Ibuprofen	1	<0.03[d]	<0.3[d]		64
Ibuprofen	1	0.008[g]	0.09		65
Indomethacin	16	<0.01-1.48		1.2	66
Ketorolac	10	0.015-0.037	0.2[f]	0.2[f]	67
Lonazolac calcium[c]	5			0.2 (LC) 0.7 (M-1)	68
Mefenamic acid	10	0.13-0.23[e]	1.7	2.1	69
Naproxen	1		1.1	2.8	70
Naproxen	NR	0.01			71
Piroxicam	4	0.01-0.03	1.1	5.4[f]	72
Piroxicam	2	0.009-0.014	1.8	8.9	73
Phenylbutazone	NR	0.13		8.8	74
Tenoxicam[c]	6	0.011-0.017 (TXM)	0.5 (TXM)	2.3 (TXM)	75
		0.017-0.044 (5-TXM)[h]	0.6 (5-TXM)	3.1 (5-TXM)	
Tolmetin[c]	1	0.005-0.007[h]	0.09		76

a Infant dose per kg bodyweight as a percentage of maternal dose per kg bodyweight.

b Based on cumulative amount secreted over 12 hours.

c Single dose study.

d Milk concentration below limit of detection.

e Based on mean values on days 3 and 4 of treatment.

f 10 out of 12 women had milk concentrations below limit of detection.

g Plasma samples were not drawn. Plasma concentrations used for the calculations were simulated using the mean plasma profile for the tablets used.

h Based on area under the curve values.

AA = 4-aminoantipyrine; **AAA** = 4-acetylaminoantipyrine; **EFA** = etofenamic acid; **FAA** = 4-formylaminoantipyrine; **FFA** = flufenamic acid; **LC** = lonazolac calcium; **M-1** = lonazolac metabolite; **MAA** = 4-methylaminoantipyrine; **NR** = not reported; **TXM** = tenoxicam; **5-TXM** = 5-hydroxytenoxicam.

In a 7-day-old baby whose mother was treated with naproxen 750 mg/day, prolonged bleeding time, haemorrhage and acute anaemia were observed.[81] In a study of 20 lactating mothers receiving naproxen (doses and infant ages were not reported), drowsiness was observed in 2 infants and vomiting in 1.[37] However, the assessment of causality is complex because no control group was included.

In conclusion, the limited data available suggest that the quantity of naproxen excreted into breast milk is low. However, the half-life is relatively long (10 hours) and safety when used for long term treat-

ment at high dosages has not been sufficiently elucidated. Nevertheless, the American Academy of Pediatrics considers treatment with naproxen to be compatible with breast-feeding.[50]

5.7 Piroxicam

Piroxicam has a long elimination half-life (20 to 70 hours in adults). M/P ratios and relative doses to the suckling infant are presented in table VI.[72,73] After a mother had ingested piroxicam 20mg daily for 4 months,[73] piroxicam could not be detected in serum from the infant (the limit of detection was not reported). In another suckling infant whose mother ingested piroxicam 20 to 40mg daily for a short course, neither piroxicam nor its conjugates were detected in the urine (limit of detection 15 μg/L).[72]

In conclusion, only very small quantities of piroxicam seem to be excreted into breast milk. However, since piroxicam glucuronide may be hydrolysed and absorbed in the infant, the exposure may be larger than assumed on the basis of available data.[20,44] In addition, the long half-life may be a concern during long term treatment. Because of these factors, and as limited information is available, it might be appropriate to prefer other NSAIDs during long term treatment. However, intermittent use of piroxicam could most probably be regarded as acceptable.

5.8 Tenoxicam

Tenoxicam has a long elimination half-life (approximately 70 hours in adults). The excretion of tenoxicam in breast milk has been investigated in a single high dose study.[75] M/P ratios and relative doses to the infant are shown in table VI. As the quantity of the drug excreted in breast milk is small, single or occasional use of the drug would be expected to be well tolerated. However, because data are lacking and because the half-life of the compound is long, it might be pertinent to prefer other NSAIDs during long term treatment.

5.9 Other Nonsteroidal Anti-Inflammatory Drugs

M/P ratios and relative doses to the infants for other NSAIDs are presented in table VI. Although most of these drugs are excreted in breast milk in small or very small amounts, the clinical significance of these quantities is not known.

Flurbiprofen has a short elimination half-life (3 hours in adults) with inactive metabolites, and the calculated maximum relative dose to the infant is low (table VI).[61,62] Consequently, the use of flurbiprofen is usually regarded to be compatible with breast-feeding.[44,78] For flufenamic acid,[60] mefenamic acid[69] and ketorolac,[67] all with elimination half-lives of 4 to 6 hours, the infant ingests less than 1% of the maternal dose (table VI). Consequently, the risk to the suckling infant seems to also be low for these drugs. However, if it is de-

Table VII. Concentrations of nonsteroidal anti-inflammatory drugs in plasma from suckling infants

Drug	Number of cases	Maternal dosage (mg/day)	Infant age	Infant plasma concentration (mg/L)	Reference
Dipyrone	1	1500[a]	42 days	3.2[b,c]	78
Indomethacin	7	75-300	<10 days	<0.020-0.047[d]	66
Piroxicam	1	20	13 months	-[e]	73
Phenylbutazone	Not reported	750[f]	Not reported	3-20	74

a The mother ingested 500mg of dipyrone on 3 occasions during 24 hours.

b Sample was obtained 24 hours after the last intake of dipyrone.

c Adverse effects reported (see section 5.9).

d In 6 out of 7 infants the plasma concentration was below the limit of detection.

e Plasma concentration was below the limit of detection (limit of detection not given in the report).

f Intramuscular administration.

cided to give mefenamic acid to a lactating mother, the suckling infant should be monitored for diarrhoea, a frequent adverse effect of this drug.

Several other NSAIDs are excreted into breast milk in small quantities (table VI). The adverse effect profile of these drugs will, however, limit their use in lactating mothers. Azapropazone[55] has been associated with a high frequency of renal, hepatic, allergic and haematological adverse reactions. Dipyrone[57] has been associated in adults with serious reactions such as agranulocytosis. Moreover, cyanotic crisis was observed in a 42-day-old breast-fed infant whose mother had ingested 3 500mg doses of dipyrone.[78] The serum concentration of dipyrone was of the same order of magnitude in the infant as in the mother (table VII). Phenylbutazone is not recommended for use in lactating mothers because of its toxicity, the long elimination half-life (49 to 142 hours in adults) and the fact that it has been found in serum of breast-fed infants (table VII).[74] Fenbufen[59] should probably also be avoided in lactating mothers because of the high frequency of skin rashes and the risk for serious skin reactions.

6. Excretion of Opioid Analgesics in Breast Milk

6.1 Codeine

M/P ratios and relative doses to the infant for codeine and its active metabolite morphine are presented in table VIII,[36,83] and drug concentrations

Table VIII. Milk/plasma concentration ratios and relative doses to the suckling infant for opioid analgesics

Drug	Number of cases	Milk/plasma concentration ratio	Relative dose to the suckling infant (%)[a]		Reference
			maximum in a feed	maximum in a day	
Butorphanol	12	0.7-0.8[b]	0.24[b]		82
		1.7-2.2[c]	0.14[c]		
Codeine	2	2.16 (COD)[d]	0.80 (COD)	0.61 (COD), 0.09 (MOR)[e]	36
		2.46 (MOR)[d]			
Codeine	7		1.1 (COD) 0.07 (MOR)[e]		83
Fentanyl	13	2.10[f]	0.92		84
Fentanyl	10			1.7	85
Ketobemidone	5	8.9	1.5		86
Morphine	5	2.45±0.8[g]	7.0[h]		87
Morphine	6			0.9	88
Pethidine (meperidine)	9	1.07-1.20 (PET)	0.87 (PET)[h]		89
Pethidine	5			2.5 (PET + NPE)	88
Pethidine	2	0.82-1.59 (PET) 0.68-6.13 (NPE)			90
Pethidine	8		2.7 (PET)[h]		91
Propoxyphene	6	0.42 (PRO)		0.57 (PRO), 1.62 (NPR)[i]	92, 93
		0.38 (NPR)			

a Infant dose per kg bodyweight as a percentage of maternal dose per kg bodyweight.

b Intramuscular administration to the mother.

c Oral administration to the mother.

d Based on area under the curve values from 1 individual.

e Percentage of the maternal codeine dose.

f Mean 0.75 hours after intravenous administration to the mother.

g Mean ± SD.

h Parenteral administration to the mother.

i Percentage of the maternal propoxyphene dose.

COD = codeine; **MOR** = morphine; **NPE** = norpethidine (normeperidine); **NPR** = norpropoxyphene; **PET** = pethidine (meperidine); **PRO** = propoxyphene.

Table IX. Concentrations of opioid analgesics in plasma from suckling infants

Drug	Number of cases	Maternal dosage (mg/day)	Infant age (days)	Infant plasma concentration (mg/L)	Reference
Codeine	11	60-720[a]	1-5	<0.8-4.5 (COD) <0.5-2.2 (MOR)[b]	83
Morphine	1	40[c]	21	4	94

a Cumulative dose; daily dosage or duration of treatment not reported.

b 1 to 4 hours after breast-feeding, which took place 1 hour after intake of codeine 60mg.

c Oral administration to the mother.

COD = codeine; **MOR** = morphine.

measured in the infant are shown in table IX. Codeine is metabolised to morphine by the polymorphic enzyme CYP2D6,[12] which is inactive in a certain proportion of the population (see section 2.1).[13] As the pharmacological activity of codeine is considerably less than that of morphine, the milk and infant concentrations of morphine might be more relevant than the concentrations of codeine.[95] However, the possibility of infant metabolism from codeine to morphine argues that the sum of codeine plus morphine in milk is the more relevant measurement for drug exposure. The metabolic fate of morphine in the infant, including the role of the morphine glucuronides, is discussed in section 6.5.

Infant plasma morphine concentrations after maternal treatment with codeine are, as a maximum, 2 to 4% of the concentrations found to be toxic in infants.[95] Moreover, these concentrations represent 8 to 18% of the suggested minimum effective analgesic dose in infants.[96,97] Consequently, breast-feeding could most probably be considered as being compatible with codeine intake. However, as only 4 mothers received more than 4 doses of codeine 60mg,[83] possible effects of long term exposure have not been fully elucidated.

6.2 Propoxyphene

M/P ratios and relative doses to the infant for propoxyphene and its metabolite norpropoxyphene are presented in table VIII.[92,93] The maximum concentrations in breast milk after a total intake of dextropropoxyphene hydrochloride 390mg over 16 hours were found to be 210 μg/L for propoxyphene and 606 μg/L for norpropoxyphene.[92] Because it was most likely that norpropoxyphene had not reached steady-state in that study because of its long half-life, it might be excreted in even larger amounts during long term treatment. Moreover, because norpropoxyphene is cleared by renal elimination, it cannot be excluded that significant amounts of this compound may arise in the suckling infant during long term maternal treatment. However, during short term treatment it seems unlikely that the suckling infant will be exposed to doses that will cause any detrimental effects.

6.3 Butorphanol

M/P ratios and relative doses to the infant for butorphanol are presented in table VIII. In the only published study,[82] butorphanol tartrate was given in single doses of 2mg intramuscularly or 8mg orally during the first days after delivery, and maternal serum and milk concentrations were studied 1, 3 and 6 hours after drug administration. No drug effects were observed in the infants. On the basis of the low doses excreted in milk, breast-feeding appears to be acceptable after single maternal doses of butorphanol. No data exist on the possible effects after repeated administration, but as butorphanol is mainly excreted by the kidneys it cannot be excluded that detrimental effects may arise after long term treatment.

6.4 Ketobemidone

M/P ratios and relative doses to the infant for ketobemidone are presented in table VIII. In the only published study,[86] ketobemidone was given in doses of 5 or 10mg subcutaneously after caesarean section (3 patients) or for curettage 12 to 15 days

after delivery (2 patients). Maternal serum and milk concentrations were studied 3 to 9 hours after drug administration. The maximum absolute dose to the infant in a meal can be estimated to be 1.1 μg/kg bodyweight. As the oral bioavailability of ketobemidone at least in adults is low (approximately 35%) the absorbed dose in infants might be lower than the ingested dose. Thus, it seems reasonable to believe that administration of single doses to the mother will not cause any detrimental effect in the infant. However, the number of infants exposed is low and long term studies or systematic evaluations of possible adverse effects have not been carried out.

6.5 Morphine

The first studies on the excretion of morphine into breast milk were published in the 1930s.[38,98] In these studies, employing insensitive and nonselective analyses with limits of detection about 2.5 mg/ml, none or only trace amounts were detected in milk. During the last decade several new studies on this topic have been published.[87,88,99] M/P ratios and relative doses to the infant for morphine based upon these studies are presented in table VIII and infant concentrations are shown in table IX.

In one study, the excretion of morphine was followed for up to 6 hours after epidural, intravenous or intramuscular administration.[87] The maximum peak concentration in milk was 500 μg/L and appeared 0.5 hours after administration of 10mg intravenously plus 5mg intramuscularly. In this case the maximal ingested dose to the infant in a meal would be 15 μg/kg. The morphine concentration in milk fell rapidly and was below 20 μg/L 6 hours later.

In a case report,[94] a woman with systemic lupus erythematosus was treated with oral morphine 200 mg/day during the third trimester and until 1 week after delivery. The drug was gradually tapered down over 10 days and the day before the study day the patient received 40mg. The maximum morphine concentration in milk the next day was 100 μg/L. The infant serum concentration was 4 μg/L (table IX). This is below the suggested minimum effective analgesic concentration in infants[96,97] but it is within the concentration range reported to exert analgesia in older children.[97] No symptoms attributable to morphine exposure were observed in the infant, but it cannot be excluded that the infant had developed tolerance to morphine as a result of the long term intrauterine exposure.

The excretion of morphine and pethidine (meperidine) in breast milk has been compared in 2 studies.[88,99] In the first of these,[88] 5 mothers received morphine intravenously and later perorally, starting immediately after delivery. Morphine and morphine-3-glucuronide concentrations in breast milk reached peaks of around 60 and 25 μg/L, respectively, between 24 and 48 hours after delivery (mean cumulative morphine dose around 160mg at 48h) and then declined. At the third day of life, each neonate was evaluated with the Brazleton Neonatal Behavioural Scale. On relevant subscales, neonates in the morphine group scored significantly better than neonates in the pethidine group (see section 6.6). In the second study,[99] 102 parturients received morphine or pethidine intravenously as patient-controlled analgesia starting after umbilical cord clamping. On the third and fourth days of life, infants in the morphine group were significantly more alert and oriented than those in the pethidine group. The average cumulative maternal opioid consumption was equivalent in the 2 groups; morphine 0.54 mg/kg *vs* pethidine 4.7 mg/kg.

In conclusion, treatment with single doses of morphine to the mother will not be expected to cause any detrimental effects in suckling infants, although the role of the active metabolite morphine-6-glucuronide has not been studied. The oral bioavailability of morphine has not been investigated in infants, but in older children it ranges from 17 to 67%.[100] If the bioavailability in infants is in the same order of magnitude, or lower, the absorbed dose could be lower, or considerably lower, than the ingested dose. Morphine has been shown to be preferable to pethidine for the infant when used at delivery.[88,99] Although there is a lack of data for later times post partum, it seems reasonable to prefer morphine in all lactating women.

However, as infants have impaired hepatic and renal functions, one cannot exclude that significant concentrations of morphine and the morphine glucuronides may arise in the suckling infant during long term maternal treatment. Thus, the importance of uninterrupted breast-feeding should, in such cases, be assessed on an individual basis against the potential risk of adverse drug effects in the infant. If it is decided to continue breast-feeding, the infant should be observed for possible adverse effects.

6.6 Pethidine (Meperidine)

M/P ratios and relative doses for pethidine and its active metabolite norpethidine to the infant are presented in table VIII.

In a study of 9 lactating mothers,[89] pethidine 50mg intramuscularly produced a mean peak concentration in breast milk of 130 μg/L 2 hours later. The highest peak concentration was 207 μg/L. After 24 hours, the mean concentration had decreased to 20 μg/L. According to this study the maximum dose to the infant in a feed would be 6.2 μg/kg. In another study in 8 lactating mothers,[91] the maximum peak concentration of pethidine was 318 μg/L 2 to 4 hours after administration of 25mg intravenously. According to this study, the maximum dose to an infant in a feed would be 9.5 μg/kg.

The excretion of morphine and pethidine in breast milk has been compared in 2 studies.[88,99] In the first of these,[88] 5 mothers received pethidine intravenously and later perorally, starting immediately after delivery. The mean pethidine concentration in breast milk reached a peak of >1000 μg/L at 12 hours after delivery (mean cumulative dose 350 to 400mg) and then declined to about 200 μg/L at 48 hours (mean cumulative dose around 1000mg); however, the norpethidine concentration took 48 hours to reach peak values of around 500 μg/L and then remained stable until 72 hours. The persistent elevated concentrations of norpethidine in breast milk, together with the long elimination half-lives of pethidine and norpethidine in neonates (table II), may cause significant plasma concentrations of norpethidine in infants. Such an accumulation could explain the fact that neonates whose mothers received pethidine had more neurobehavioural depression than neonates whose mothers received morphine.[88] This finding has recently been confirmed in another study including a total of 102 mothers[99] (see also section 6.5).

In conclusion, the risk to the suckling infant seems to be negligible after a single dose of pethidine. As the oral bioavailability, at least in adults, is low (approximately 50%), the absorbed dose in infants might be lower than the ingested dose. However, the metabolite norpethidine was not measured in the single dose studies.[89,91] Nevertheless, the concentration of this metabolite is most probably low after single doses. In contrast, it has been demonstrated that repeated doses of pethidine may affect suckling infants negatively.[88,99] This phenomenon is most probably caused by the relatively high milk concentrations of pethidine, and particularly of the active metabolite norpethidine, in addition to the slow elimination of these compounds in infants (table II).

6.7 Fentanyl

The excretion of fentanyl in milk has been investigated in 2 studies.[84,85] In one of these,[84] 13 women were given fentanyl citrate 2 μg/kg intravenously during caesarean section or for tubal ligation postpartum. Serum and colostrum were collected for 10 hours. As expected, the concentrations in milk were highest at the initial sampling 45 minutes after administration (mean 0.40 μg/L; range 0.08 to 0.97 μg/L). M/P ratios and relative doses to the infants at this time are presented in table VIII. Thereafter, the milk concentrations decreased rapidly and were virtually undetectable (the limit of detection was not reported but was apparently lower than 0.01 μg/L) after 6 hours.

In the second study,[85] milk was collected 4 and 24 hours after the last dose from 10 women treated with a total of fentanyl citrate 50 to 400mg intravenously during labour. In most of the milk samples the concentrations of fentanyl were below the limit of detection (<0.05 μg/L). In a few samples, the concentrations were between 0.05 and 0.15 μg/L

both after 4 and after 24 hours. According to these data, a suckling infant would ingest maximally 1.7% of the bodyweight-adjusted maternal dose per day. It is, however, remarkable that the milk concentrations should be stable during such a long time interval. One may, therefore, speculate that this is an artefact due to methodological errors, although extremely slow elimination combined with variations in the milk triglyceride content might also possibly explain the findings. On a neurobehavioural examination within the first 24 hours of life, all infants had normal scores.

The low concentrations in breast milk are consistent with the short elimination half-life in adults (table II). Although fentanyl is sometimes very slowly cleared from neonates,[26] the small dose in milk will hardly cause any adverse effects in the infant. Thus, breast-feeding could presumably be regarded as acceptable after the administration of single doses to the mother. However, no studies have been carried out during long term fentanyl treatment.

7. Conclusions

The issue of whether breast-feeding should be discouraged or not during treatment with analgesics is clinically important, but in many cases is also very complex because of the lack of data and the methodological limitations of the published reports. Moreover, our lack of knowledge about the concentrations at which there is absolutely no pharmacological effect in the infant complicates the risk analysis even more, as do doubts about the generalisability of the findings from a few individuals to the population of all infants and from short term treatment to long term treatment. It should, however, be remembered that drug exposure through breast milk is generally very limited compared to intrauterine exposure if the mother has been treated with the same drug during pregnancy.

It is important that the potential risks to the infant during maternal treatment with analgesics are put into the right perspective. Specifically, breast milk clearly has nutritional, immunological and other advantages over formula milk, but the possible negative effects of not receiving breast milk are rarely considered. In general, if treatment of a lactating mother with an analgesic drug is considered necessary, a drug that is minimally excreted in breast milk and has had widespread use without association with detrimental effects in the infant should be preferred. The lowest effective maternal dose should be given, and the dose to the infant can be further reduced if breast-feeding is avoided at times of peak drug concentration in milk. For drugs where available data do not warrant absolute recommendations, the potential risks to the infant should be carefully weighed on an individual basis against the benefits of continuing breast-feeding. The risk-benefit discussion should preferably also be presented to the mother who, based on her assessment of the importance of the different compounds in the risk-benefit analysis, could contribute to the final decision.

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