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Anticonvulsant Use During Lactation

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Abstract

The issue of prescribing anticonvulsant drugs during lactation is clinically important, but also complex. Data for some drugs are completely lacking and for other drugs information is only available from single dose or short term studies or case reports. Moreover, limited knowledge exists about the practical impact of the drug concentrations found in breast milk and there are great methodological problems in the assessment of possible adverse drug reactions in infants. Nevertheless, based on current knowledge, some recommendations can be suggested.

Treatment with carbamazepine, valproic acid (sodium valproate) and phenytoin is considered compatible with breastfeeding. Treatment with ethosuximide or phenobarbital (phenobarbitone)/primidone should most probably be regarded as potentially unsafe and close clinical monitoring of the infant is recommended

if it is decided to continue breastfeeding. Occasional or short term treatment with benzodiazepines could be considered as compatible with breastfeeding, although maternal diazepam treatment has caused sedation in suckling infants after short term use. During long term use of benzodiazepines, infants should be observed for signs of sedation and poor suckling. Only very limited clinical data are available for the new generation anticonvulsant drugs and no clearcut recommendations can be made until further data are present. If it is decided to continue breast feeding during treatment with these drugs, the infant should be monitored for possible adverse effects.

In general, the drug should be given in the lowest effective dose, guided by maternal serum or plasma drug concentration monitoring. If breast feeding is avoided at times of peak drug levels in milk, the exposure of the infant can be reduced to some extent. As breast milk has considerable advantages over formula milk, the benefits of continuing breast feeding should always be taken into consideration in the risk-benefit analysis.

The positive effects of breast feeding are well established. Breast milk has nutritional advantages over formula milk, and contains enzymes that promote digestion and absorption of nutrients. Breast milk causes 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] Breast feeding is inexpensive and has advantages of simplicity and portability. For the nursing mother, suckling stimulates postnatal uterine involution, and long duration of breast feeding protects against breast cancer.[7] Breast feeding is also an important opportunity to enhance the mother-child interaction quality. Taken these advantages into account, it is essential that possible risks to the infant during maternal drug treatment are carefully weighted 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 anticonvulsants into breast milk is based on single dose or short term studies, and for many drugs, only 1 or a few case reports have been published. Moreover, although very low drug concentrations can be measured in breast milk with modern analytical techniques, there is also generally a lack of knowledge about the practical importance of these low drug concentrations. Another methodological concern is that great problems arise in the assessment of adverse drug reactions in neonates and infants. It is often not possible to separate potential drug effects, which on the basis of the dose in milk often are presumed as subtle and unspecific, from the normal state of the infant, or from concurrent disease. Moreover, no studies have addressed the possible long term effects of anticonvulsant exposure through breast milk. However, a recent review article[8] on possible cognitive and behavioural effects when the infants and children themselves were treated with anticonvulsants suggests that most individuals do not experience clinically relevant behavioural effects. Given all these limitations, it is not surprisingly that conclusive data and, thereby, unambiguous recommendations, are lacking for many drugs.

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

1. Literature Search

A literature search of the databases Medline and Embase using the terms ‘milk’ and ‘lactation’ for pa-

pers written in all languages was executed for all compounds included in this review. Moreover, original research articles, previously published review articles and textbooks were scrutinised in order to identify publications not picked up by the original database searches.

2. Factors Influencing Drug Excretion into Breast Milk

The most important single factor accounting for the great interindividual pharmacokinetic variability that exists for many drugs is the oxidative liver enzyme capacity, which is predominantly genetically determined. Phenytoin and diazepam are mainly metabolised by the cytochrome P450 (CYP) enzymes CYP2C9 and CYP2C19, respectively. The activities of these enzymes are bimodally distributed in the population. Thus, an individual can be classified as an extensive metaboliser or a poor metaboliser for each of these enzyme activities. The prevalence of CYP2C9 poor metabolisers is less than 1%,[9] whereas the prevalence of CYP2C19 poor metabolisers varies from 3 to 21% according to race.[10] If the mother or the infant, or both, are poor metabolisers, a standard dose to the mother will result in higher than average drug concentration in the nursed infant with an assumed increased risk for adverse effects.

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 influences the total drug concentration in breast milk. For example, for drugs that are bound to plasma proteins to a relatively high degree, such as phenytoin, valproic acid (sodium valproate) and clobazam, the excretion into milk tends to be relatively low. In contrast the excretion into milk for drugs that are bound to plasma proteins to a low degree, such as ethosuximide tends to be relatively high.

As the triglyceride content is higher in breast milk than in plasma, drugs with a high lipid solubility, such as clonazepam and other benzodiazepines, tend to concentrate in milk. Moreover, as the triglyceride content is higher in mature milk than in colostrum and higher in hind-milk than in fore-milk, 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.[11,12] In addition, the total lipid content also varies considerably between feeds and between individuals.[13]

Milk has a lower pH than plasma, with variations from 6.6 to 7.0.[14] As only the nonionised fraction of any molecule is transferred readily across the milk/plasma membrane, milk concentrations of weak acids, such as valproic acid, phenytoin and phenobarbital (phenobarbitone), tend to be lower than the concentrations of weak bases.

3. Calculation of Drug Dose to the Infant

The milk/plasma drug concentration ratio is a frequently used quantitative measure of the translactal passage of a drug. The milk/plasma ratio for a given drug may, however, vary with regard to milk pH, milk triglyceride and milk protein content.[15] 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.[15] Ideally, milk/plasma ratios should therefore be based on area under the curve calculations, or at least on multiple pairs of samples, obtained at the equilibrium of distribution.

The ingestion of milk by a suckling infant generally amounts to about 150ml per kg per 24 hours.[14] In the present review, this volume is used in the calculations of the drug amounts ingested by the infant. However, considerable variations exist. For example, in 8 to 13 day old male infants, variations in milk intake from 122 to 208ml per kg per 24 hours have been observed.[16]

When the maternal plasma drug concentration and the milk/plasma ratio are known, the daily dose to a suckling infant can be estimated as the product of the maternal drug concentration in plasma, the milk/plasma 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 in milk, such as carbamazepine-10,11-epoxide, 10-hydroxyoxcarbazepine, desmethylclobazam, desmethyldiazepam and oxazepam 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.

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.[17,18] In preterm and full term neonates and infants, these parameters may differ markedly from the corresponding values in children and adults. Thus, although in general infants are exposed to a higher dose of a drug when they are *in utero* than when they are breastfed, the immature systems for metabolism and excretion of drugs in an infant could cause relatively high concentrations postnatally. Available data on the elimination of anticonvulsants in neonates in comparison with adults are presented in table I.

For most drug-metabolising 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 the order of magnitude of 2 to 6 times that in adults. For drugs with enzyme-inducing properties, such as carbamazepine and phenobarbital, the metabolic rate in the neonate may be in the adult range if the mother has been treated with the same drug during pregnancy. The ability to perform glucuron-

Table I. Elimination half-lives of anticonvulsants in adults and neonates[18-22]

Drug	Half-life in adults (hours)	Half-life in neonates (hours)
Classical anticonvulsants		
Carbamazepine	15 ± 5[a,b,c] (5-26[b,c,d])	8-37[d,e]
Oxcarbazepine	1-3[d]	22[f]
10-hydroxyoxcarbazepine[h]	8-15[d]	17[f]
Phenobarbital (phenobarbitone)	99 ± 18[a,b]	148 ± 55[a,e] (100-500[d,e])
Phenytoin	6-60[i]	2-140[d,e,f,i]
Valproic acid (sodium valproate)	14 ± 3[a,c,j]	9-49[c,d,j]
Benzodiazepines		
Clonazepam	23±5[a]	140[f] (22-43[d,g])
Diazepam	20-65[d]	400[f]
Desmethyldiazepam[k]	50-100[d]	8-140[d]
Oxazepam[k]	4-10[d]	22
Midazolam	2	7 (23[f])
New generation anticonvulsants		
Vigabatrin	5-7[d]	5-11[d]

a Mean ± SD.
b Induces its own metabolism.
c Value given is after multiple doses.
d Range.
e May be in the adult range if the mother has been treated with the same drug during pregnancy.
f Maximum occurs in the first days post partum.
g In older infants.
h Active metabolite of oxcarbazepine.
i Varies according to the actual concentration due to nonlinear kinetics.
j Inhibits its own metabolism.
k Active metabolite of diazepam.

ide conjugation reactions in neonates is impaired to an even greater extent than the oxidative metabolic capacity.[23,24] This fact might have some impact on the metabolism of drugs that are extensively glucuronidated in the liver, such as lamotrigine and valproic acid.

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.[17,24] Tubular function is even more impaired in neonates, and reduced tubular function may persist up to 6 to 9 months of age.[17,24] However, the capacity for renal excretion is of minor importance for the elimination of anticonvulsants with the exception of 10-hydroxyoxcarbazepine, gabapentin and vigabatrin.

5. Excretion of Classical Anticonvulsants

5.1. Carbamazepine

The excretion of carbamazepine and its active metabolite carbamazepine-10,11-epoxide has been investigated in several studies. Milk/plasma ratios and relative doses for carbamazepine and its active metabolite are presented in table II. The elimination half-life of carbamazepine is moderately longer in neonates than in adults (table I). However, in infants whose mothers have been treated with carbamazepine during the pregnancy, half-lives in the adult range have been found.[55]

Carbamazepine concentrations have been measured in the plasma of a few suckling infants. These concentrations generally amount to approximately 1.0 μg/ml, but concentrations up to 4.8 μg/ml have been reported (table III). All mothers described in these reports received treatment with carbamazepine during pregnancy and some of the positive assays may therefore, at least in part, be caused by transplacental passage of the drug. The dose of carbamazepine ingested by the neonate is nevertheless less than 6% of the recommended initial therapeutic paediatric dosage of 10 to 20 mg/kg/day and the infant serum concentrations found are in general less than 20% of the recommended therapeutic concentrations in adults.

Adverse effects in suckling infants have been described, but there is only 1 report[26] of such an effect exclusively related to carbamazepine exposure via breast milk. Poor suckling was observed in 1 of a series of 15 breast fed infants whose mothers were receiving carbamazepine monotherapy.[26] In other reports, the adverse effects described may be related both to translactal and transplacental passage of the drug. Transient cholestatic hepatitis, a well known complication of carbamazepine treatment, was observed in a 3-week-old infant exposed to the drug both during pregnancy and breast feeding.[56] Hepatic dysfunction, characterised by hyperbilirubinaemia and high concentrations of γ-glutamyl transferase, was observed the first day of life in an infant whose mother was treated with carbamazepine during pregnancy and during breast feeding.[57] The symptoms resolved after the frequency of breast feeding was decreased at 9 days postpartum, despite continued maternal carbamazepine treatment. In a 4-week old infant exposed concomitantly for carbamazepine, phenytoin, primidone and phenobarbital, poor suckling, bodyweight gain and drowsiness were observed.[31] Drowsiness was also noticed in a 10-week-old fully breast fed infant whose mother was treated with clemastine, phenytoin and carbamazepine.[32] The infant's drowsiness was, however, ascribed the clemastine treatment due to the close time relationship between the maternal treatment and the symptom duration.

The American Academy of Pediatrics[58] considers carbamazepine to be compatible with breast feeding and similarly the World Health Organization Working Group on Drugs and Human Lactation[14] concludes that the use of carbamazepine is 'probably safe'. Based on the relatively low infant plasma concentrations, the risk that drug exposure through breast milk should cause detrimental effects seems small. No information is available for the closely related compound oxcarbazepine.

Table II. Milk/plasma concentration ratios and relative doses to the suckling infant for conventional anticonvulsants

Reference	No. of cases	Milk/plasma concentration ratio	Relative dose to the suckling infant[a](%)
Carbamazepine			
Kuhnz et al.[25]	4	CBZ = 0.20-0.95; CBZ-E = 0.13-0.80	2.1-8.0
Froescher et al.[26]	16	CBZ = 0.25-0.58; CBZ-E (n = 4) = 0.34-0.63	CBZ = 1.6-4.7; CBZ + CBZ-E (n = 5) = 3.3-5.7
Pynnönen et al.[27]	3	CBZ = 0.63; CBZ-E = 0.9	CBZ + CBZ-E = 4.1-7.2
Pynnönen & Sillanpää[28]	1	CBZ = 0.6; CBZ-E = 0.6-1.0	CBZ + CBZ-E = 3.3
Niebyl et al.[29]	1	CBZ = 0.24-0.39	CBZ = 2.4[c]
Kaneko et al.[30]	3[e]	CBZ = 0.39 ± 0.19[d]	[b]
Kaneko et al.[31]	25[e]	CBZ = 0.41 ± 0.17[d]	[b]
Kok et al.[32]	1	CBZ <1	CBZ = 2.4[c]
Brent & Wisner[33]	1	CBZ = 0.07	CBZ = 0.4
Wisner & Perel[34]	1	CBZ = 0.15	[b]
Ethosuximide			
Koup et al.[35]	1	0.94 ± 0.06[d]	54
Kaneko et al.[30]	4[e]	0.79 ± 0.33[d]	[b]
Rane & Tunell[36]	1	0.80 ± 0.06[d]	115
Kuhnz et al.[37]	5	0.77-1.0	32-74
Söderman et al.[38]	4	0.79-1.03	[f]
Phenobarbital (phenobarbitone)			
Kaneko et al.[30]	8[e]	0.46 ± 0.25[d]	350[g]
Kaneko et al.[31]	59[e]	0.36 ± 0.20	350[g]
Kuhnz et al.[39]	13	0.36 ± 0.09[d]	[b]
Westerink & Glerum[40]	8	0.11-0.29	37
Primidone			
Niebyl et al.[29]	1	PD = 0.48-0.59; PB = 0.28-0.29	PD + PB = 13
Kaneko et al.[30]	12[e]	0.81 ± 0.18[d]	[b]
Kaneko et al.[31]	51[e]	0.70 ± 0.18[d]	[b]
Nau et al.[41]	4	PD = 0.40-0.86; PB = 0.32-0.60; PEMA = 0.50-0.94	PD + PB + PEMA = 38
Söderman et al.[42]	2	PD = 0.67-0.96; PB = 0.33-0.46	PD = 18
Kuhnz et al.[39]	7	0.72 ± 0.20[d]	[b]
Phenytoin			
Steen et al.[43]	6	0.06-0.18	10.4
Kaneko et al.[30]	9[e]	0.18 ± 0.06[d]	[b]
Kaneko et al.[31]	59[e]	0.19 ± 0.16[d]	[b]
Rane et al.[44]	1	0.45	[b]
Shimoyama et al.[45]	5	0.13-0.52	6.8
Mirkin et al.[46]	2	0.15-0.69	9.1
Valproic acid (sodium valproate)			
Froescher et al.[26]	5	0.01-0.07	[b]
Von Unruh et al.[47]	11	0.01-0.10	3.8
Dickinson et al.[48]	1	0.01-0.02	0.4
Alexander[49]	1	0.05-0.10	2
Nau et al.[50]	6	0.03	7.0
Nau et al.[51]	13	0.025 ± 0.01[d]	[b]
Bardy et al.[52]	1	<0.02-0.06	3.5
Philbert et al.[53]	1	0.02-0.10	[b]
Tsuru et al.[54]	2	0.02-0.03	2.6-3.1

a Infant dose per kg bodyweight expressed as a percentage of maternal dose per kg bodyweight. Based on worst case analysis.
b Maternal dose not reported.
c The active metabolite carbamazepine-10,11-epoxide not included in the calculations.
d Mean ± standard deviation.
e Number of samples or number of cases not stated.
f Milk concentrations not reported.
g Calculations based on the maternal dose reported during pregnancy.

CBZ = carbamazepine; **CBZ-E** = carbamazepine-10,11-epoxide; **PB** = phenobarbital; **PD** = primidone; **PEMA** = phenylethylmalonamide.

5.2 Ethosuximide

Ethosuximide appears in breast milk at concentrations nearly equal to those in maternal plasma and the calculated relative doses to the suckling infant are high (table II). The daily dose received by the infant is estimated to be between 4 and 11 mg/kg, which is about 10 to 60% of the recommended therapeutic dose for younger children of 20 to 30 mg/kg. Plasma ethosuximide concentrations in suckling infants have ranged between 15 and 40 μg/ml, which is close to the therapeutic range of 40 to 100 μg/ml recommended for adults.

Hyperexcitability was observed during the first 2 weeks in a newborn who was nursed for 10 days and whose mother was receiving ethosuximide monotherapy.[37] In addition, sedation, poor suckling and hyperexcitability was described in 4 out of 6 infants nursed by mothers treated with ethosuximide.[37] However, 3 of these mothers were also treated with other anticonvulsants such as carbamazepine, clonazepam, primidone, phenobarbital and valproic acid, which were suspected to have contributed to the symptoms.

Whereas ethosuximide is considered compatible with breast feeding by the American Academy of Pediatrics,[58] the World Health Organization Working Group on Human Lactation[14] regards the use of the drug during lactation as unsafe. Based on the high plasma concentrations found in suckling infants and the reports of adverse effects, breast feeding should most probably be regarded as potentially unsafe. Close clinical monitoring of the infant, supported by monitoring of maternal serum concentrations, is recommended if it is decided to continue breast feeding during maternal ethosuximide treatment.

5.3 Phenobarbital (Phenobarbitone) and Primidone

Milk/plasma ratios and relative doses for phenobarbital and primidone, which is partly metabolised to phenobarbital, are presented in table II. The ingested absolute dosage of phenobarbital may reach 2 to 5 mg/day which corresponds to a relative bodyweight-adjusted dose of at least 13% of the maternal dose. Phenobarbital is slowly excreted by infants, and therefore infant plasma concentrations may reach or even exceed the maternal concentrations (table III).

Adverse effects in infants whose mothers received treatment with phenobarbital have been known at least since 1926.[59] In another early study, sedation was observed in 2 out of 41 infants whose mothers received treatment with phenobarbital.[60] Poor sucking and a high incidence of vomiting have also been observed in breast fed newborns whose mothers received primidone, phenobarbital or other anticonvulsant treatment.[31] In addition, drowsiness, poor suckling and bodyweight gain were observed in an infant exposed to carbamazepine, phenytoin, primidone and phenobarbital.[31] Drug-induced sedation was suspected to be a contributory cause to the death of a infant nursed by a mother who was treated with phenobarbital and primidone.[61] The blood concentration of phenobarbital found in the infant postmortem was 8.3 μg/ml. In another case, methaemoglobinaemia, anaemia, haemorrhages, drowsiness and poor suckling was observed in suckling newborn whose mother was receiving treatment with phenobarbital and phenytoin.[62] Intense drowsiness was again observed in the infant when breastfeeding was restarted. Moreover, a series of infantile spasms was observed in a breast fed infant whose mother was treated with phenobarbital, primidone and carbamazepine after abrupt weaning.[63] No further seizures were observed in the infant during 6-months' treatment with phenobarbital or a 5-year follow-up period.

There is no consensus regarding the recommendations for lactating mothers treated with phenobarbital and primidone. The American Academy of Pediatrics[58] recommends that phenobarbital and primidone should be used with caution during lactation whereas the World Health Organization Working Group on Drugs and Human Lactation[14] classifies the use of these drugs as unsafe during breast feeding. One reviewer[64] has suggested alternating breast feeding and bottle feeding as a pos-

Table III. Plasma concentrations of conventional anticonvulsants in suckling infants

Reference	No. of cases	Maternal dose (mg/day)	Infant age (days)	Infant plasma concentration (μg/ml)[a,b]	Maternal plasma concentration (μg/ml)
Carbamazepine					
Kuhnz et al.[25]	3	10-22 mg/kg/day	5-28	0.5-4.7	8.8 (n = 1); NR (n = 2)[c]
Froescher et al.[26]	3	15-18 mg/kg/day	4-7	0.1-<1.5	7.1-8.5
Pynnönen et al.[27]	2	NR	28-35	CBZ = 0.5-1.8; CBZ-E = 0	CBZ = 2.6-3.1; CBZ-E = 0.5-1.1
Pynnönen & Sillanpää[28]	1	8 mg/kg/day	30	1.8	CBZ = 3.1; CBZ-E = 1.0
Kok et al.[32]	1	800	70	0.5-1.0	4
Brent & Wisner[33]	1	500	90	0.7	4.7
Ethosuximide					
Rane et al.[36]	1	500	7-140	9-30	44-66
Kuhnz et al.[37]	5	NR	4-30	15-40	28-84[c]
Söderman et al.[38]	4	1000-1050	NR	24-75%[d]	NR
Phenobarbital (phenobarbitone)					
Kuhnz et al.[39]	1	275	10-30	7-9	20-25
Primidone					
Kuhnz et al.[39]	1	500	10-25	PD = 0.7-0.9; PB = 2; PEMA = 0.4	PD = 7-12; PB = 6-8; PEMA = 2-4
Kuhnz et al.[39]	1	325-625	28-50	PD = 0.7-2; PB = 7-9; PEMA = 1	PD = 4-10; PB = 20-28; PEMA = 7-8
Nau et al.[50]	2	7.6 mg/kg/day	14-21	PD = 0.8-1.0; PB = 1.5-3.0; PEMA = 0.5-0.6	PD = 6.0-9.7; PB = 5.5-8.9; PEMA = 2.7-3.2
Söderman et al.[42]	1	500-1000	NR	PB = 2[c]	PD = 11-28
Phenytoin					
Kok et al.[32]	1	300	70	<0.5	5
Valproic acid (sodium valproate)					
Wisner & Perel[34]	1	750	30	4	65
Nau et al.[50]	2	27-31 mg/kg/day	11	0.50-0.55	NR
Bardy et al.[52]	1	600	60	0.4-2.0	18-34

a Suggested therapeutic concentration ranges (adults): carbamazepine 5-10 μg/ml; ethosuximide 40-80 μg/ml; phenobarbital 10-30 μg/ml; phenytoin 10-20 μg/ml; valproic acid 50-100 μg/ml.

b Conversion factors from μg/ml to μmol/l 4.2 for carbamazepine, 7.1 for ethosuximide. 4.3 for phenobarbital, 4.0 for phenytoin, 6.9 for valproic acid.

c Adverse effects reported (see section 5).

d Percent of average maternal concentration.

CBZ = carbamazepine; **CBZ-E** = carbamazepine-10,11-epoxide; **PB** = phenobarbital; **PD** = primidone; **PEMA** = phenylethylmalonamide; **NR** = not reported.

sible successful strategy to minimise the infant's drug exposure. Monitoring phenobarbital concentrations in exposed infants has also been recommended.[65,66] Based on the relative high exposure to the breast fed infant and the reported adverse effects in exposed neonates, lactation should be regarded as potentially unsafe. Women who decide to breast feed their infants should be instructed to observe the infant for possible drug effects, such as sedation and poor suckling.

5.4 Phenytoin

Phenytoin is excreted in breast milk in relatively small quantities. Milk/plasma ratios and the relative doses are presented in table II, and drug concentrations in the infant are shown in table III.

Available estimates indicate that the amount of phenytoin that a suckling infant would ingest is less than 11% of the bodyweight-adjusted maternal daily dose. Moreover, the calculated infant dosage (0.03 to 0.47 mg/kg/day) is less than 5% of a typical therapeutic infant dosage of 10 mg/kg/day.

In a suckling infant exposed for phenytoin and phenobarbital, drowsiness, poor suck swallow coordination and methaemoglobinaemia was observed,[63] and in another suckling infant exposed to carbamazepine, phenytoin, primidone and phenobarbital, sedation, poor suckling and bodyweight loss was noted.[31] The authors considered the treatment with phenytoin as the main cause of the symptoms in these 2 cases, although it cannot be excluded that the other drugs may have contributed.

The American Academy of Pediatrics[58] regards phenytoin as compatible with breast feeding and the World Health Organization Working Group on Human Lactation[14] concludes that the use of this drug during lactation may be regarded as safe. A significant risk to the breast fed infant seems unlikely considering the low concentrations found in breast milk.

5.5 Valproic Acid (Sodium Valproate)

Valproic acid is excreted in human milk in low concentrations and the estimated maximum bodyweight-adjusted relative daily dose to a suckling infant is 4% (table II). The elimination half-life of valproic acid is clearly prolonged in neonates (table I). Infant plasma concentrations reported are shown in table III. Based on available data, the dose to the suckling infant can be estimated to be less than 6% of the recommended initial paediatric therapeutic dosage of 20 mg/kg/day. In a case report,[49] the serum concentration of valproic acid at delivery was about the same in the suckling infant as in the mother, but fell to insignificant concentrations after 5 days and was undetectable (limit of detection not stated) after 29 days, despite an adequate maternal plasma concentration of 80 μg/ml. In an additional study,[53] the serum concentration in a 3-month-old suckling infant was 7.6% of the maternal serum concentration. In a recent report, a breast fed infant whose mother was treated with valproic acid developed thrombocytopenic purpura and anaemia; recovery was complete after withdrawal of the treatment.[67] The authors consider it possible that the maternal valproic acid treatment might have caused the haematological adverse effects in the infant.

The American Academy of Pediatrics[58] and the World Health Organization Working Group on Human Lactation[14] classify valproic acid as compatible with breast feeding, although others have suggested that breast feeding should be avoided because of the potential risk of severe hepatotoxicity.[68] However, no cases of liver toxicity in suckling infants have been reported. Although, 1 report of haematological abnormalities in an infant possibly related to transfer of valproic acid exposure through breast milk warrants caution, the exposure through breast milk is very low compared with the recommended dosage for the treatment of seizures in infants and children. Thus, no dose-dependent adverse effects should be expected in the infant.

6. Excretion of Benzodiazepines

6.1 Clobazam

After short term administration, clobazam and its active metabolite desmethylclobazam are transferred into breast milk in small quantities (table IV). However, as the elimination half-lives are approximately 24 hours for the parent compound and 40 hours for the metabolite, infant exposure is expected to be slightly higher after multiple doses. The infant would receive at most, 10% of the usual therapeutic paediatric dosage of 0.5 mg/kg/day (range 0.1 to 1 mg/kg/day) used in the treatment of seizures.

The World Health Organization Working Group on Human Lactation[14] considers clobazam to be safe if the maternal dose is low and if the exposure is short. However, during long term administration, the infant should be monitored for possible detrimental effects, such as sedation and poor suckling.

Table IV. Milk/plasma concentration ratios and relative doses to the suckling infant for benzodiazepines

Reference	No. of cases	Milk/plasma concentration ratio	Relative dose to the suckling infant (%)[a]
Clobazam			
Bennett[14]	6	CLO + DCLO = 0.13-0.36	CLO + DCLO = 11.5
Clonazepam			
Söderman & Matheson[69]	1	0.13	5
Fischer et al.[70]	1	0.33	[b]
Diazepam			
Erkkola & Kanto[71]	3	DIA = 0.10-0.13; DDIA = 0.08-0.11	DIA + DDIA = 4.5[c]
Wesson et al.[72]	1	DIA = 0.13-0.21; DDIA = 0.10-0.52	DIA + DDIA = 2.9[c]
Brandt[73]	4	DIA = 0.13-0.18; DDIA = 0.19-0.35	DIA + DDIA = 13.4[c]
Sundsbak et al.[74]	2	DIA = 0.11-0.58; DDIA = 0.08-0.34	DIA + DDIA = 2.6[c]
Dusci et al.[75]	1	DIA = 0.2; DDIA = 0.13	[c]
Cole & Hailey[76][d]	9	DIA + DDIA 0.21-2.77 (Mean 0.5 DIA + DDIA)	[c]
Lorazepam			
Whitelaw et al.[77]	1	NR	7.1[e]
Summerfield et al.[78]	4	0.15-0.26	[c]
Midazolam			
Matheson et al.[79]	2	0.09-0.16	MID + HMID = 1
Nitrazepam			
Matheson et al.[79]	9	0.28 ± 0.06[f]	2.6

a Infant dose per kg body weight as a percentage of maternal dose per kg body weight. Based on worst case analysis.

b Maternal dose not reported.

c The active metabolites temazepam and oxazepam were not included in the calculation.

d Not studied under steady-state conditions.

e Assuming that all lorazepam glucoronide in milk is deconjugated (see section 4).

f Mean ± standard deviation.

CLO = clobazam; **DCLO** = desmethylclobazam; **DDIA** = desmethyldiazepam; **DIA** = diazepam; **HMID** = α-hydroxymidazolam; **MID** = midazolam; **NR** = not reported.

6.2 Clonazepam

Milk/plasma ratios and relative doses to the infant for clonazepam are presented in table IV. In a case report, a serum concentration of 2.9 ng/ml was measured in a 7-day-old suckling infant (table V).[70] However, since the half-life of clonazepam is thought to be prolonged in neonates, a significant part of this concentration is most likely a consequence of exposure *in utero*. The infant experienced persistent apnoea spells until 10 weeks of age. The authors recommend that infants exposed to clonazepam through breast milk should be monitored for CNS depression and apnoea. As the relative dose of diazepam to the infant is in the same magnitude as for that for which sedation has been reported (see section 6.3), it seems pertinent to observe the infant closely.

6.3 Diazepam

Diazepam has a long elimination half-life (table I) and active metabolites (desmethyldiazepam, temazepam and oxazepam). Milk/plasma ratios and relative doses to the infant for diazepam are shown in table IV and drug concentrations in the infant are shown in table V. Diazepam and desmethyldiazepam are excreted into breast milk, producing milk/plasma ratios typically of 0.1 to 0.5. The calculated relative dose ingested by an infant is less than 14% of the maternal dose. Thus, the infant would at most receive about 5% of the therapeutic paediatric dosage of 0.5 mg/kg/day.

Sedation, bodyweight loss, electroencephalogram changes and mild jaundice were observed in a 1-week-old baby, whose mother had been treated for 3 days with diazepam 30 mg/day.[80] Milk and infant concentrations of diazepam were not determined, but the metabolite oxazepam was detected in the urine of the neonate. Based on this case, it has been suggested that diazepam in daily doses of 30mg or above should be avoided in lactating mothers, while daily doses of 10mg or less should not pose a significant risk for the suckling infant. However, in another case report,[72] sedation was observed repeatedly when the infant was breast fed less than 8 hours after a maternal dose of diazepam when the mother was treated with diazepam 6 to 10 mg/day.

In conclusion, detrimental effects in the suckling infant may arise during maternal treatment with diazepam, although very sparse data exist to claim that infants exposed to diazepam via breast milk only, without any additional exposure during pregnancy or delivery, run a high risk of adverse effects. On the other hand, available studies do not adequately address the issue of long term treatment. The American Academy of Pediatrics[58] considers the effects of benzodiazepines on the breast fed infant to be unknown but possibly of concern. Based on current knowledge breast feeding can be regarded to be safe when 1 or a few single doses are given for acute seizure control. However, if very high doses are given, discarding milk during the first 24 hours after treatment should be considered. During prolonged treatment with diazepam, the infant should be observed for signs of sedation and poor suckling. If high doses have to be used, and particularly if long term administration is required, breast feeding should probably be discontinued.

6.4 Lorazepam

The excretion of lorazepam in breast milk appears to be small (table IV).[77,78] Although a potential cause of feeding problems, maternal lorazepam use was not associated with a significant decline in the volume of milk consumed or duration of feeding in exposed infants.[77]

The World Health Organization Working Group on Human Lactation[14] classifies short term use of lorazepam as probably safe. Based on the low amounts of lorazepam reaching the infant, treatment with the drug seems to be compatible with breast feeding. However, caution should be taken if high doses have to be used or if long term treatment is required.

Table V. Plasma concentrations of benzodiazepines in suckling infants

Reference	No. of cases	Maternal dose (mg/day)	Infant age (days)	Infant plasma concentration (ng/ml)	Maternal plasma concentration (ng/ml)
Clonazepam					
Fischer et al.[70]	1	NR	5-14	1.0-2.9[b]	19[c]
Diazepam					
Erkkola & Kanto[71]	3	30	4	DIA = 172 ± 5[a]; DDIA = 243 ± 8[a]	DIA = 491 ± 56[a]; DDIA = 340 ± 59[a]
Erkkola & Kanto[71]	3	30	6	DIA = 74 ± 10[a]; DDIA = 31 ± 6[a]	DIA = 601 ± 22[a]; DDIA = 483 ± 32[a]
Wesson et al.[72]	1	6-10	NR	DIA = 0.7; DDIA = 46	DIA = 100; DDIA = 200
Dusci et al.[75]	1	DIA = 25; OXA = 15	1 year	DIA <5; DDIA = 21; OXA = 7.5; TEM = 7	DIA = 1000; DDIA = 1000; OXA = 300; TEM = 100
Dusci et al.[75]	1	DIA = 35	1 year	DIA <5; DDIA = 20; OXA = 9.6; TEM = 7	DIA = 1400; DDIA = 900; OXA = 300; TEM = 100

a Mean ± standard deviation.

b Adverse effects reported (see section 6).

c Sample obtained at delivery. Therapeutic range in adults 5-70 ng/ml.

DDIA = desmethyldiazepam; **DIA** = Diazepam; **NR** = not reported; **OXA** = oxazepam; **TEM** = temazepam.

Table VI. Milk/plasma concentration ratios and relative doses to the suckling infant for new generation anticonvulsants

Reference	No. of cases	Milk/plasma concentration ratio	Relative dose to the suckling infant (%)[a]
Gabapentin			
Data on file[83]	5	0.7 ± 0.1[b]	[c]
Lamotrigine			
Tomson et al.[84]	1	0.6	10
Rambeck et al.[85]	1	0.35-0.68	21
Berry[86]	NR	0.4-0.8	[c]
Öhman et al.[87]	9	0.47-0.77	[c]
Vigabatrine			
Tran et al.[88]	2	0.04-0.22[d]	1.0[d]
		0.14-0.87[e]	3.6[e]

a Infant dose per kg bodyweight as a percentage of maternal dose per kg body weight. Based on worst case analysis.

b Mean ± standard deviation.

c Maternal dose not reported.

d Calculated for the S enantiomer which is pharmacologically active.

e Calculated for the R enantiomer which is pharmacologically inactive.

NR = not reported.

6.5 Midazolam

Midazolam is excreted into breast milk in small amounts (table IV). During repeated once daily administration with this short acting drug (elimination half-life 2 hours and 2-5 hours for its active metabolite α-hydroxymidazolam) no day-to-day increase in drug concentrations in milk was observed and no measurable concentrations (limit of detection 2 ng/ml) were found approximately 7 hours after intake of an oral 15mg dose.[79]

Based on the short elimination half-life, the small quantities excreted into breast milk and the absence of reported adverse effects in exposed infants, the drug seems compatible with breast feeding. The World Health Organization Working Group on Drugs and Human Lactation[14] regards short term use while breast feeding as probably safe.

6.6 Nitrazepam

Data from 9 lactating mothers indicate that small amounts of nitrazepam are excreted in breast milk (table IV). During repeated administration milk concentrations will gradually increase due to the long elimination half-life of this compound (27 to 30 hours). The mean milk concentration in 5 mothers receiving nitrazepam 5mg at night increased from 8.4 ng/ml the first morning to 13.5 ng/ml the fifth morning.[79] The plasma level of nitrazepam in 1 exposed infant was below the limit of detection (<3 ng/ml) on day 5 of drug administration.

The World Health Organization Working Group on Drugs and Human Lactation[14] concludes that short term use of nitrazepam appears safe. However, during long term treatment the nursed infant should be monitored for signs of sedation and poor suckling.

7. Excretion of New Generation Anticonvulsants

7.1 Felbamate

No studies have been published on the excretion of felbamate in breast milk. According to the manufacturer, the excretion of felbamate into breast milk has been documented in 1 case.[81] Due to the serious adverse effects that have been observed in adults,[82] such as aplastic anaemia and acute liver failure and the lack of detailed information about the quantities of the drug excreted into breast milk, women treated with felbamate should not breast feed.

7.2 Gabapentin

The excretion of gabapentin has been studied in healthy individuals, resulting in milk/plasma ratios about 0.7 (table VI).[83] Until more data is available, gabapentin should be used with great caution in lactating mothers and the infant should be monitored for possible adverse effects such as sedation and poor suckling.

7.3 Lamotrigine

Milk/plasma ratios and relative doses to the suckling infant for lamotrigine are presented in table VI and infant concentrations are shown in table VII. In a case report[85] in which a mother was treated with lamotrigine during late pregnancy and lactation, infant samples during the first 5 months postpartum revealed therapeutic lamotrigine concentrations. The authors estimated that between 2 and 5mg lamotrigine per day was excreted in the breast milk. In a second case report,[84] the infant plasma concentration was approximately 25% of the concentration in maternal plasma. The authors estimated the daily dose ingested by the exposed infant to be about 0.5 mg/kg/day. For comparison, a typical paediatric maintenance dosage of lamotrigine for treatment of seizures is 1 to 5 mg/kg/day. No adverse effects were observed in either of the exposed infants described above.

The limited data available indicate that infant lamotrigine concentrations may reach levels at which pharmacological effects may be expected. If it is decided to continue breast feeding, the infant should be monitored for possible adverse effects such as sedation and poor suckling.

7.4 Vigabatrin

In 2 lactating mothers milk/plasma ratios for the pharmacologically active S-enantiomer of vigabatrin were 0.04 to 0.2 (table VI)[88]. Until more data is available, treatment with vigabatrin should be used with great caution in nursing mothers and infant should observed for possible adverse effects such as sedation and poor suckling.

7.5 Other New Generation Anticonvulsants

No data are available on the excretion of tigabine, topiramate or zonisamide in human breast milk or on possible effects on infants exposed for these drugs via breast milk. Until data are available, no specific recommendations can be made.

8. Conclusions

The issue of whether breast feeding should be discouraged or not during treatment with anticonvulsants is clinically important but, particularly for the newer agents, also very complex, because of lack of data and methodological limitations of the published reports. Moreover, the incomplete knowledge about the concentrations at which there is absolutely no pharmacological effect in the infant, and about the generalisability of the findings from a few case reports or studies to the population of all infants complicates the risk analysis even more.

In general, the drug should be given in the lowest effective dose. The maternal concentrations and if possible also infant concentrations should be monitored, and the maternal drug concentrations should be kept as low as advisable within the therapeutic range. If breast feeding is avoided at times of peak drug concentrations in milk, the exposure to the nursed infant can be further reduced to some

Table VII. Plasma concentrations of new generation anticonvulsants in suckling infants

Drug	No. of cases	Maternal dose (mg/day)	Infant age (days)	Infant plasma concentration (μg/ml)	Maternal plasma concentration (μg/ml)
Lamotrigine					
Tomson et al.[84]	1	300	14	1.4	5.6
Rambeck et al.[85]	1	200-300	11-64	1.5-2.7	4.3-9.6

extent, particularly for drugs with short elimination half-lives.

It is important that the potential risks to the infant during maternal treatment with anticonvulsants are put into the right perspective. Specifically, breast milk clearly has nutritional, immunological and other advantages over formula milk, but the possible risks of not receiving breast milk are rarely considered. Therefore, when currently available data do not warrant absolute recommendations, the potential risks to the infant during maternal treatment with anticonvulsants should be carefully weighed against the benefits of continuing breast feeding. The risk-benefit discussion could in such cases preferably also be presented for 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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