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Lactation studies of anticonvulsants: a quality review

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AIM
The aim of this review was to investigate the quality of the current literature on the transfer of anticonvulsants to breast milk to provide an overview of which anticonvulsants are in need of further research.

METHODS
We reviewed the quality of the available lactation studies for 19 anticonvulsants against the guidelines of the Food and Drug Administration (FDA) and the International Lactation Consultant Association (ILCA).

RESULTS
Except for one study on lamotrigine and one case report on gabapentin, no study on anticonvulsants had both the absolute infant dose (AID) and milk to plasma ratio (M : P) correctly assessed. Only one study on carbamazepine, phenytoin and vigabatrin was found that correctly assessed the AID. The main cause for this low number is the lack of essential details in published studies, since 25 of 62 studies were case reports, letters or abstracts. Other major shortcomings were the lack of information on sampling methods, the number of samples in a particular dose interval as well as the low number of study participants.

CONCLUSION
The quality of the current literature on the transfer of anticonvulsants to breast milk is low, except for lamotrigine, which makes it hard to draw conclusions about the safety of the use of anticonvulsants during the lactation period. Therefore, further research is needed.

Introduction

Breastfeeding a child is the natural way to provide infants with essential nutrients. Human milk stimulates gastrointestinal function and improves host defences in the newborn [1–3]. Because of its overall benefits and low costs for the developing world, the World Health Organization recommends breastfeeding exclusively during the first 6 months and as supplement up to 2 years of age. In the United States, 75% of mothers have ever breastfed their infant in the early post-partum period and 36% are exclusively breastfeeding at 3 months [4]. One of the concerns in the lactation period is the safety of drugs being used by mothers, because transfer of the drug to the infant can occur through breastfeeding and may lead to adverse effects. This accounts especially for women with epilepsy, who often need long term anti-epileptic drugs to prevent seizures. In the United States nearly 1.1 million women with epilepsy are of the childbearing age [5]. Drowsiness, sedation, hepatitis, apnoea, methaemoglobinaemia and withdrawal symptoms are some of the reported adverse effects of anticonvulsant drug exposure in breast milk [6–11]. The long half-life of anticonvulsants in infants is another risk factor for developing adverse effects, since the drugs are not rapidly excreted [12]. Therefore, it is of great value to make a risk assessment of the possible

adverse drug reactions but to not unnecessarily withhold infants of the great benefits of breast milk. A major element of this risk assessment is the estimated dose an infant receives through breastfeeding, as can be found in guidelines of the Food and Drug Administration (FDA) and the European Medicine Agency (EMA) [13, 14]. The other three major elements of risk assessment are infant plasma concentrations, observed adverse effects of the infant and follow-up of breast fed infants. This review focuses on the first element, the estimated infant dose and is not easily answered since studies about the pharmacokinetic and pharmacodynamic behaviour of anticonvulsant drugs in human milk vary in study design. Furthermore, the used methodology is in general not congruent with the International Lactation Consultant Association (ILCA) and FDA guidelines. Both guidelines provide a clear overview on the parameters which have to be determined to make a statement on the transfer of drugs into the breast milk and the infant. The absolute infant dose (AID) is considered as an informative and practical endpoint for the estimated dose an infant receives. The AID is defined as the dose an infant receives by ingestion of maternal milk after one single maternal dose or during a dose interval at steady-state. The milk to plasma ratio (M : P) is an estimate of the distribution of the drug between maternal plasma and milk. Recommendations to determine the AID and/or the M : P ratio are stated in these guidelines. We performed a literature review for lactation studies that measured the amount of anticonvulsants in breast milk and checked whether they met the ILCA and FDA guidelines on lactation studies to provide an overview of which anticonvulsants are in need of further research.

Methods

Anticonvulsants of interest

The following anticonvulsants are registered in the Netherlands: carbamazepine, clobazam, clonazepam, eslicarbazepine, ethosuximide, gabapentin, lacosamide, lamotrigine, levetiracetam, oxcarbazepine, phenobarbital, phenytoin, primidone, retigabine, rufinamide, stiripentol, topiramate, valproic acid and vigabatrin.

Inclusion of studies

The LactMed database was used to include studies. LactMed is part of the National Library of Medicine's (NLM) Toxicology data network and provides information about drug concentrations in breast milk and infant blood (http://lactmed.nlm.nih.gov). This database contains also information on possible adverse effects in breast fed infants. All data are peer reviewed and continually updated. LactMed is considered as one of the most accurate and extensive sources on information about drugs in breastfeeding mothers [15].

Drug records on LactMed contain a 'drug concentrations' segment in which findings of studies that reported amounts of drugs in breast milk are numerated. All studies in this 'drug concentration' segment were included in this review.

A Pubmed search was carried out to reveal any missing articles. The following query was used: ('Milk, Human'[Mesh] OR 'Breast Milk'[title/abstract] OR 'Human Milk'[title/abstract]) AND ('carbamazepine'[All Fields] OR 'clobazam'[All Fields] OR 'clonazepam'[All Fields] OR 'eslicarbazepine'[All Fields] OR 'ethosuximide'[All Fields] OR 'gabapentin'[All Fields] OR 'lacosamide'[All Fields] OR 'lamotrigine'[All Fields] OR 'levetiracetam'[All Fields] OR 'oxcarbazepine'[All Fields] OR 'phenobarbital'[All Fields] OR 'phenytoin'[All Fields] OR 'primidone'[All Fields] OR 'retigabine'[All Fields] OR 'rufinamide'[All Fields] OR 'stiripentol'[All Fields] OR 'topiramate'[All Fields] OR 'valproic acid'[All Fields] OR 'vigabatrin').

Searches in LactMed and Pubmed were performed during December 2013. All studies published until then were eligible for inclusion. Studies that did not measure breast milk concentrations or any anticonvulsant of interest were excluded. Books were also excluded since they are not original research. Studies written in other languages than English, Dutch or German were excluded as well.

Criteria for quality review

The quality review of all studies was based on the ILCA and FDA protocol [13, 14]. These protocols with guidelines on lactation studies, topics on study design, the amount of drugs in breast milk and determination of kinetics were merged to create a checklist (Table 1) and each study was checked using this checklist if it met the criteria. To characterize further the type of studies included, we stated if studies were case reports, letters, abstracts or full articles.

Results

A total number of 62 articles was included for review (Figure 1). Using the LactMed database, we found 61 studies. One more article was added to this with the use of the PubMed query described in the methods section. The average number of investigated anticonvulsants per study was 1.20. Sixteen of the 62 studies were case reports, case series or letters and nine studies were abstracts. No studies were included for eslicarbazepine, retigabine, rufinamide, stiripentol, clobazam and lacosamide. Only one study was included for pregabalin and vigabatrin.

The results of our review are shown in Table 2. Regarding the endpoints, the AID was correctly assessed in one study for carbamazepine (three patients), phenytoin (one patient), gabapentin (one patient) and vigabatrine (two

Table 1

Quality checklist based upon the FDA and ILCA protocol

Subject	Criterion
Publication status	No criterion: Registered type of study: full article, case report / letter or abstract
Study design	
Median number of patients (min–max)	No criterion: Registered number of included patients (and of which milk samples were obtained)
Longitudinal design	Obtained milk samples at multiple days post-partum in same patient
Amount of drug in breast milk	
Dose	Daily dose of patient is given
Timing of dose	Time between drug intake and milk sampling is given
Milk samples	Obtained pre- and post-feed samples OR total milk collection of one feeding and took aliquot for analysis
Determination of kinetics	
Milk concentrations	Obtained at least five milk samples in one dose interval
Plasma concentrations	Obtained at least five plasma samples in one dose interval
Active metabolites	Measured active metabolites, if any
Infant plasma	Obtained one plasma sample from nursed infant
Endpoints	
Milk : plasma ratio (M : P)	Correctly assessed if M : P is calculated from AUC in milk and plasma based on ≥ 5 milk and plasma levels
Absolute infant dose (AID)	Correctly assessed if entire volumes of milk in 24 h were collected OR by collecting ≥ five milk samples in dose interval

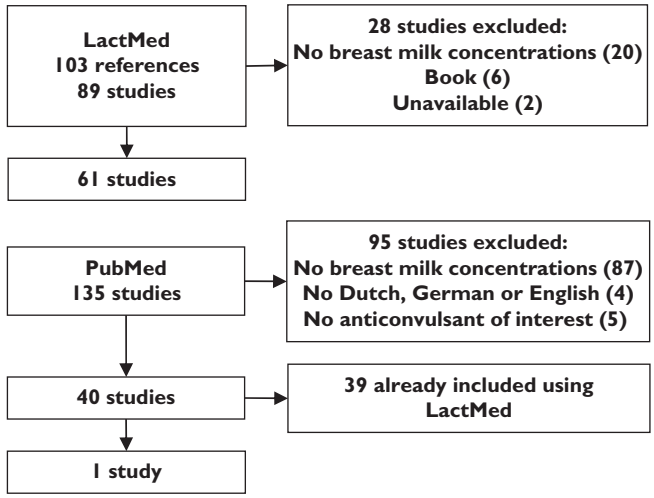

Figure 1

Results of study inclusion using LactMed and Pubmed

patients) and in two studies for lamotrigine (total of 29 patients). The milk to plasma ratio (M : P) was correctly determined in one study for lamotrigine (six patients) and gabapentin (one patient).

Discussion

Our review showed that no anticonvulsant had both the AID and M : P correctly assessed according to the guidelines of the FDA and ILCA, except for one study on lamotrigine [16] and a case report on gabapentin [17]. Regarding the AID lamotrigine [18], carbamazepine [19], phenytoin [20] and vigabatrin [21] had only one study that assessed the AID correctly. Despite our results, these data are used in risk assessments worldwide every day. One of the reasons for this low number is that the ILCA and FDA protocols were not yet available as guidance, since most studies were published between 1970 and 2000. Another contributing factor for this low number is the publication status, since many studies have never been fully published. Therefore, most quality criteria could not be determined due to the brief character of the reports. This also accounts for the large number of case reports and letters that reported maternal milk concentrations.

As described in our results section, the number of participants in the studies that had the AID or M : P correctly assessed was low. Although the FDA and ILCA protocols do not mention a minimum number of study participants it is hard to state if the results of such small studies are representative for the whole group of lactating mothers. Even more some of these studies are case reports which are susceptible to selection bias due to their retrospective character.

The description of milk sampling was lacking for most studies. It was therefore not possible to take the drug distribution into account and the measured concentration could either be in foremilk, hindmilk or both. Because of the higher lipid content of hindmilk, lipophilic drugs will be more present at the end of feeding [22]. Studies that analyzed fore and hindmilk separately, showed that drug concentrations of some antidepressants were two to four times as high in post-feed compared with pre-feed samples [23, 24].

Most studies only obtained one milk sample in a dose interval. The time milk samples were obtained with respect to dose intake was not reported in most studies. Studies investigating kinetics in milk samples showed that drug concentrations in milk vary during the dose interval, with the highest drug concentrations in the first half of the dose interval [25–28]. If only one sample is taken and/or the time of sampling to dose intake is not stated, the actual and calculated absolute infant dose may differ. A large number of studies did not report the ingested dose. Without this dose, interpreting the AID or reported breast milk concentration is impossible since both depend on the maternal dose.

Table 2

Results of quality review. All numbers represent the number of articles that matches corresponding criterion in Table 1

	Carbamazepine [8, 19, 40–49]	Ethosuximide [41, 45, 50–54]	Phenobarbital [20, 41, 55–58]	Phenytoin [20, 41, 45, 59–64]	Lamotrigine [10, 16, 18, 65–72]	Valproic acid [45, 73–79]	Pregabalin [80]	Clonazepam [9, 63]	Gabapentin [17, 81, 82]	Levetiracetam [83–86]	Oxcarbazepine [87–89]	Primidon [41, 42, 45, 58, 90]	Topiramate [91–93]	Vigabatrine [21]
Number of studies included	**12**	**7**	**6**	**9**	**11**	**8**	**1**	**2**	**3**	**4**	**3**	**5**	**3**	**1**
Publication status														
Abstract	2	2	0	0	4	0	1	0	1	2	1	0	1	0
Case report/letter	5	1	1	2	3	3	0	2	1	0	1	2	0	0
Full article	5	4	5	7	4	5	0	0	1	2	1	3	2	1
Study design														
Median number of patients (min–max)	3 (1–56)	2 (1–5)	8 (1–13)	3 (1–9)	6 (1–34)	4 (1–13)	2 (2–2)	1 (1–1)	3 (1–5)	12.5 (7–14)	1 (1–3)	7 (1–12)	1 (1–3)	2 (2–2)
Longitudinal design	7	3	3	4	3	5	0	2	0	2	2	3	1	0
Amount of drug in breast milk														
Daily dose	10	5	2	7	7	8	0	1	2	3	2	3	3	1
Time of drug intake until sampling	1	2	4	6	5	4	0	1	1	2	2	0	1	1
Representative milk samples	2	1	0	2	2	0	0	1	1	0	0	1	1	1
Determination of kinetics														
Milk concentrations	0	0	0	1	2	0	0	0	1	0	0	0	0	0
Plasma concentrations	0	0	0	0	1	0	0	0	0	0	0	0	0	0
Active metabolites	5	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	2	N/A	N/A	N/A
Infant plasma	7	3	3	5	9	5	1	2	3	3	3	2	1	0
Endpoints														
M : P correctly assessed	**0**	**0**	**0**	**0**	**1**	**0**	**0**	**0**	**1**	**0**	**0**	**0**	**0**	**0**
AID correctly assessed	**1**	**0**	**0**	**1**	**2**	**0**	**0**	**0**	**1**	**0**	**0**	**0**	**0**	**1**

Values in bold correspond to endpoints.

AID, Absolute infant dose; M : P, Milk : plasma ratio; N/A, Not applicable.

The absolute exposure of anticonvulsants in the suckling infant can be revealed by measuring infant serum concentrations and is, beside the infant dose, another major element in the risk assessment according to the EMA [29]. Although this review only included studies in which breast milk concentrations were measured, studies with infant serum concentrations but without measuring breast milk concentrations were also found [30–38]. Most of these studies were either abstracts or case reports and were not correlated to the ingested infant dose, making it difficult to interpret reported infant serum concentrations. Therefore, measuring infant serum concentrations should be accompanied by measuring breast milk concentrations.

Longitudinal data to minimize intra-individual measurements are taken into account for most anticonvulsants. This is important to correct for the variation of analysis and variable milk composition during the post-partum period. Lipid content and pH vary in the first few weeks which can influence the extent of drug transfer to breast milk [39].

Conclusion

The clinical importance of qualitative studies that assess the AID or M : P is to determine if observed adverse effects in breast fed infants can be the result of nursing and if these effects are dose related. For this reason the European Medicine Agency (EMA) [29] and the FDA [14] state that the infant dose is one of the major elements for a risk assessment. We showed that most studies with anticonvulsants did not provide this infant dose. Another element in the risk assessment is to provide information on how to minimize exposure of the breast fed infant to the drug. With data on the kinetics of a drug in breast milk, timing of minimum and maximum drug concentrations become known, so mothers can be instructed to feed at specific times post-dose. We conclude that the quality of the current literature about this topic is rather poor. Better studies are needed to determine the extent of drug transfer to breast milk or M : P ratio for anticonvulsants.

Competing Interests

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare no support from any organization for the submitted work. IW had financial relationships, outside the submitted work, with organizations that might have an interest in the submitted work in the previous 3 years. There are no other relationships or activities that could appear to have influenced the submitted work.

Contributors

AW and PH designed the study. DM carried out the literature review with AW and PH. DM, AW, IW, BW and PH prepared the manuscript.

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