WHEN BREASTFEEDING MOTHERS NEED CNS-ACTING DRUGS

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ABSTRACT

Background
Breastfeeding is the ideal method of infant nutrition. However, if mothers need medications such as the central nervous system (CNS) acting drugs, infant safety concerns arise. Summarized information on infant exposure levels to drugs in milk and associated side effect profiles will help clinicians to rationalize and justify important drug therapy for a breastfeeding patient.

Methods
Electronic searches of MEDLINE and PsycINFO from 1966-2003, and of EMBASE from 1980-2003, were conducted for studies on breastfeeding or breast milk and medications in the following categories: antidepressants, antipsychotics, antiepileptics (or anticonvulsants) and anxiolytics. The infant exposure level (%) was defined as follows: [Drug concentration in milk (mg/mL)] x [Daily milk intake (mL/kg/d)] x 100 / Maternal dose (mg/kg/d).

Results
A total of 129 papers were eligible for analyses. Our findings indicate that the majority of the CNS-acting drugs, if taken by nursing women, result in average exposure levels to their breast-fed infants of less than 10% of the therapeutic doses per kg body weight. Exceptions are lithium, ethosuximide, phenobarbital, primidone, lamotrigine and topiramate. Adverse effect profiles do not always correlate with a higher exposure level. Overall, most reported adverse effect profiles appear benign. Where adverse effects were reported, they were often confounded by intrauterine exposure.

Conclusions
CNS-acting drugs taken by the mother do not appear to pose any major risks of immediate adverse effects to the breastfeeding infant, although with most of the newer drugs further research is needed to be conclusive.

Key Words: Breastfeeding, breast milk, CNS-acting drugs, psychotropic drugs, exposure levels, adverse drug reactions

Breastfeeding is the ideal method of infant nutrition. Exclusive breastfeeding for the first six months of life is strongly encouraged.[1,2] The many benefits of breastfeeding in infants include a decreased risk of diarrhea, otitis media, urinary tract infections, and necrotizing enterocolitis. Reduced incidence of inflammatory bowel disease and type I diabetes mellitus, and higher cognitive neurodevelopment are also reported in breast-fed infants.

A recent survey showed approximately 80% of Canadian women initiated breastfeeding.[3] However, if mothers need medications, safety concerns arise. Although almost all drugs are excreted in milk, there are only a few absolute contraindications to breastfeeding, and cessation

of breastfeeding is rarely required.[4,5] Drugs are excreted into milk by passive diffusion and carrier-mediated processes.[6] The amount of drug excreted in breast milk depends on its pharmacokinetic factors, including ionization, plasma protein binding, molecular weight and lipophilicity. Drugs with a cationic nature, low plasma protein binding, low molecular weight, and high lipophilicity tend to be excreted into milk more than those without such characteristics.[7]

The amount of drug the breast-fed infant would ingest via milk per unit time is almost invariably lower than therapeutic doses for the infant, mostly around 1-10% of the infant therapeutic dose.[5] Such a low level exposure is unlikely to cause a dose-dependent effect.[8] However, these so-called "exposure levels" vary among drugs even in the same therapeutic category.[9] Information about infant exposure levels will help clinicians to rationalize and justify important drug therapy for a breastfeeding patient.

In addition, knowledge about adverse events in the breast-fed infants, and the number of the patient-infant pairs studied and reported in the medical literature will serve as a foundation of the clinical risk assessment. The central nervous system (CNS) acting drugs are among the most commonly queried medications during pregnancy and lactation.[10] However, safety information regarding these drugs for lactating women and their breast-fed infants has not been reviewed thoroughly, which makes clinical risk assessment difficult. In this article we will provide a quick reference for infant exposure levels to CNS-acting drugs in milk and a summary of reported adverse events.

METHODS

Electronic searches of MEDLINE and PsycINFO were conducted from 1966-2003, and of EMBASE from 1980-2003. Original papers and review articles on breastfeeding or breast milk, and medications in the following categories: antidepressants, antipsychotics, antiepileptics (or anticonvulsants) and anxiolytics were queried.

Specific drug names were also queried along with either breastfeeding, breast milk or lactation. All articles of human studies involving the respective drugs, in the English or French language were retrieved. Both infant exposure levels and adverse drug reactions in breast-fed infants were recorded.

The infant exposure level (%) was defined as follows: [Drug concentration in milk (mg/mL)] x [Daily milk intake (mL/kg/d)] x 100 / Maternal dose (mg/kg/d).[11]

Our assumptions and operative procedures are as follows:

a) a daily milk intake of 150mL/kg[8],

b) the highest reported drug concentration in milk for the patient was used in the calculations (i.e. worst-case analysis), and

c) the mother's weight was assumed to be 65 kg wherever unreported.

All studies describing adverse events in the infant, or lack thereof, were used for adverse effect analyses. A study was excluded if the exposure was not at steady state. Review papers[4,5,7,12-24] were used for confirmation of calculations and sample size and for information on studies.

RESULTS

Our MEDLINE search produced 345 original papers and review articles. A further analysis of references from review articles produced three papers published before 1966. Of the 348 articles, 123 papers were eligible for analyses: 11 for exposure level calculations only; 29 for adverse drug reaction information only, and 83 for both. We also identified 16 review papers. The EMBASE and PsycINFO searches produced an additional three papers. The majority of the CNS-acting drugs, if taken by nursing women, result in exposure levels in their breast-fed infants of less than 10% of the therapeutic doses per kg body weight (Table 1).

TABLE I Exposure Levels[a] and Summary of Adverse Drug Reactions in Nursing Infants of Mothers Treated with a CNS-acting Medication

Drugs	Exposure Level (% of the maternal dose on a body weight basis)						Reported Adverse Drug Reactions	
	N[b]	<1	1 to <10	10 to <20	20 to <50	≥50	n/total[c]	Comments
Antidepressants ***SSRIs***								
Citalopram*[1-6]	20						1/23	One infant was reported to have reversible, concentration dependent, uneasy sleep[1]
Fluoxetine*[6-19]	61						16/181	All infants except one with reported adverse events were also exposed in utero. Six patients had spontaneous resolution[12], one infant on co-medications had transient seizure-like activity[11], three had colic[7;18], five had withdrawal symptoms[7;12;18] and one had lethargy, decreased nursing, moaning and unresponsiveness[16].
Fluvoxamine[6;20-26]	6						0/16	
Paroxetine[6;26-32]	60						0/89	
Sertraline*[6;26;33-40]	36						1/138	One study[32] had a mean inconsistent with the others (n=11); we include it here for completion; One infant was reported to have benign neonatal sleep myoclonus which spontaneously resolved and was not considered by some reports to be an adverse reaction[39]
Heterocyclics								
Amitriptyline*[41-46]	6						0/5	
Amoxapine*[47]	1						NA	
Clomipramine[45;46;48;49]	3						0/8	
Desipramine*[46;50]	1						0/2	
Doxepin*[51-53]	3						2/3	One infant had poor suck and swallow, muscle hypotonia, vomiting, drowsiness and jaundice further to in utero exposure[51] Another infant was pale, limp and drowsy with respiratory depression that resolved 24 hours after cessation of breast-feeding[53].
Imipramine*[45;46;54]	5						0/19	
Maprotiline[55]	1						NA	
Nortriptyline[46;56-59]	1						0/22	
Other								
Bupropion*[60;61]	1						0/3	
Lithium[62-66]	14						1/14	ECG changes, a cyanotic episode and lethargy were reported within the first week of birth in an infant exposed in utero; symptoms resolved after cessation of lithium[65]
Nefazodone[46;67;68]	3						1/4	An infant was drowsy, lethargic, unable to maintain normal body weight and feeding poorly [68]
Venlafaxine*[6;69-71]	9						0/15	
Antipsychotics ***Traditional***								
Chlorpromazine[72;73]	1						1/3	Drowsiness and lethargy in one infant; possible in utero exposure[72]
Chlorprothixene[74]	2						0/2	

Haloperidol[75-77]	11						3/14	Three infants displayed delayed developmental scores following in utero exposure to both haloperidol and chlorpromazine[75]
Perphenazine[78]	1						0/1	
Atypical								
Clozapine[79]	1						NA	
Olanzapine[80-82]	12						0/14	
Risperidone*[83]	1						NA	
Anxiolytics								
Alprazolam[84;85]	NA						1/6	Irritability, sleep disturbances and withdrawal following in utero expsoure[85]. One case of drowsiness reported by mother did not require medical attention and was not considered an adverse event [84].
Clonazepam[86;87]	1						1/2	Apnea (cyanosis, hypotonia, lethargy from in utero exposure); resolution at 10 days [87]
Diazepam*[88-92]	8						2/9	One reported case of lethargy and poor weight gain[90]and another case of sedation following in utero exposure[91]; both cases were reversible
Oxazepam[93]	1						NA	
Lorazepam[94]	1						0/1	
Temazepam[95]	10						0/10	Calculated using the reported detection limits
Antiepileptics ***First Generation***								
Carbamazepine[11;96-105]	29						11/31	All reported adverse reactions were secondary to in utero exposures or co-medications (mainly other antiepileptics). Transient cholestatic hepatitis seen in two infants[96;97] and transient seizure-like activity in one[11]. Hepatic dysfunction seen in one infant[98]; weakness in suckling and poor feeding seen in four infants[100;105]; hyperexcitability in two infants[105]; drowsiness, irritability, refusal to feed and high-pitched cry in one [105]
Ethosuximide[106-109]	8						3/6	All infants exposed in utero and all but one to co-medications. Two cases of hyperexcitability and one case of sedation reported[107]
Phenobarbital*[110-112]	12						NA/17	Sedation in an unspecified number of infants exposed in utero to multiple medications [110]
Phenytoin[86;113-115]	9						1/9	Methemoglobinemia in one patient also on phenobarbital with in utero exposure [115]
Primidone*[101;110;111]	5						NA/12	Sedation and feeding problems in an unspecified number of infants exposed in utero to multiple medications [110]
Valproic Acid[99;116-123]	21						1/34	Reversible thrombocytopenia and anemia in one infant with in utero exposure[117]
Second Generation								
Gabapentin[124]	2						0/2	
Lamotrigine[125-127]	11						0/11	
Topiramate[128]	3						0/3	
Vigabatrin[129]	2						NA	

= level indicating the weighted mean = level indicating the range of reported values * including active metabolite(s) NA indicates information unavailable

[a]Averages were calculated from studies meeting the inclusion criteria based on our assumptions (see methods). If no lighter shade is present, the mean fell in the same category as the entire range of values.

[b]Sample size of studies with exposure level information meeting inclusion criteria

[c]Number of infants with reported adverse events over total sample size of studies meeting inclusion criteria (includes studies which may not have available data for exposure level calculations)

DISCUSSION

Unless the infant has a substantially reduced drug elimination capacity, the exposure would seldom reach even a therapeutic level. Indeed, infants are rarely found to achieve pharmacologically significant serum concentrations of the drug.

Exceptions are found in some of the antiepileptic agents such as phenobarbital, primidone and ethosuximide. These drugs may reach an exposure level of greater than 50%. This *per se* does not mean that the infant will be adversely affected. However, other antiepileptics with favorable pharmacological profiles would be preferred. Infant exposure levels to fluoxetine in milk are mostly below 10%, and reported adverse events are transient in nature. Although the clinical significance is unclear, one study suggested that weight gain of infants exposed to the drug in milk is smaller than in the non-exposed infants.[25] Lithium may achieve exposure levels >10%, but there is only one case report of an adverse event, which was confounded by intrauterine exposure.[26] In our clinical program in Toronto, we take an individualized approach based on monitoring of drug concentration in milk.[27] Overall, women can be allowed to continue breastfeeding while receiving these drugs.

Although antidepressants have been studied extensively, there is a shortage of data on the other categories of CNS-acting drugs. In particular, newer antipsychotics such as olanzapine and risperidone are being used more frequently and merit further analysis.IndentData on long-term effects of the low-level exposure to drugs via breastfeeding is scarce. Moreover, often-associated intrauterine exposures complicate the issue. Compared with intrauterine exposure to maternal drugs, which usually reaches the therapeutic level, drug exposure via breastfeeding is considered minimal for the majority of these drugs. Health professionals should clearly communicate this fact to breastfeeding patients.

Non-adherence to chronic medications such as antidepressants may cause serious consequences. Throughout pregnancy and the lactation period, women are understandably anxious about any uncertainty surrounding the safety of their medications to their infants.

Not infrequently, they stop the necessary medications to continue breastfeeding[28] or discontinue breastfeeding altogether.[29,30] The summary provided in Table 1 is intended to be a useful tool for practitioners for assessing infant exposure levels of CNS-acting drugs in breast milk and the adverse event risks, and help them provide information to lactating mothers.

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