Drug use and breastfeeding

Summary

Background. This article describes the principles of drug transfer into breast milk and how drugs may affect breast-fed infants, and provides practical advice about what should be considered when prescribing medication for a lactating woman.

Material and method. The article is a review based on a discretionary selection of articles found after a search in PubMed, recommendations from Norwegian and international expert groups, and the authors' own studies and experience.

Results. Most recommendations concerning the use of drugs among breastfeeding women are be based on studies in which the degree of drug transfer to the mother's milk has been measured or on case studies, sometimes in combination with pharmacokinetic or pharmacodynamic considerations. However, the toxicity and dosage of the medication, duration of treatment, as well as the infant's age and health condition also need to be considered. Psychotropic drugs are the drug group for which most studies have been published. This is also the drug group for which individual risk/benefit evaluations are most often required, since a risk of pharmacological effects in the infant cannot be excluded.

Interpretation. Most drugs can be used by breastfeeding women, since the amount transferred to the breast milk is too small to exert any pharmacological effects on the infant. In most cases, the sum of available information in combination with clinical experience will be sufficient to provide specific advice about the use of medication during breast-feeding.

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During pharmaceutical treatment in the postpartum period there will often be a need to assess what drug would be the safest alternative if the woman is breastfeeding. Lack of knowledge among health personnel may result in breastfeeding women who are undergoing pharmacotherapy being instructed to wean or bottle-feed the infant, even if they use medications that will have no effect on the infant. The public in general and the mothers themselves often fear that pharmaceuticals transferred through the milk may be harmful for the infant. Since mother's milk is not only a source of nutrition but also conducive to the infant's health, significant medical reasons should be present to dissuade a mother who uses medications from breastfeeding.

The purpose of this article is to describe the principles for transfer of drugs to mother's milk and the situations in which this transfer may entail a risk of side effects in breast-fed infants, as well as to provide practical advice about how to proceed when prescription of medications to a lactating woman is considered.

Method

The article is based on the authors' experience from 15–20 years of work with pharmaceuticals and breastfeeding, as well as a discretionary selection of articles retrieved by a literature search in the PubMed database. The search was carried out on 2 November 2011. No time limit on the date of publication was set for the search. The terms «breast feeding», «breast milk» or «lactation» were linked to the search terms «medication», «drug transfer» or «drug therapy» and «adverse event» or «safety». Only English-language and Norwegian articles on safety of medication use by breastfeeding women or transfer of drugs to mother's milk were included. National guidelines and manufacturer-independent reference literature were also included in this article's knowledge base.

Of a total of 795 potentially relevant articles, 579 were excluded, since they were overlapping review articles, related to other substances than pharmaceutical drugs (viruses, environmental toxins, etc.), described animal or in-vitro studies or were methodological articles pertaining to detection of drugs in mother's milk. We refer to the book *Medications and mother's milk* (1) for a wider selection of key references.

From mother to infant

Any drug used by the mother must pass several steps (Figure 1) (1–3) to exert an effect in a breast-fed infant. The drug must be absorbed systemically in the woman to achieve a certain plasma concentration (stage 1). Drugs which are taken orally or injected are those that are most often found in the milk. Many locally acting drugs (ointments, creams, inhalational drugs, eye drops, nasal sprays, vaginal suppositories and similar) will in general not be detectable in the mother's blood in any significant concentrations, and thereby neither in her milk.

The breast is a compartment in close contact with the mother's blood. Drugs that reach a certain plasma concentration in the woman could therefore diffuse into the mother's milk (stage 2). The passage of drugs between maternal plasma and the mother's milk is based on principles of passive diffusion through lipid membranes, and will therefore invariably follow a gradient from a high to a low concentration of free

Main message

- In general, there is only a small risk of side effects in the infant when the mother uses drugs and breastfeeds.
- The risk of side effects is highest in infants younger than 2–3 months.
- Drugs that affect the central nervous system account for the largest proportion of reported side effects.
- The type of drug, the dosage, treatment time and the infant's age must be taken into account when breastfeeding.

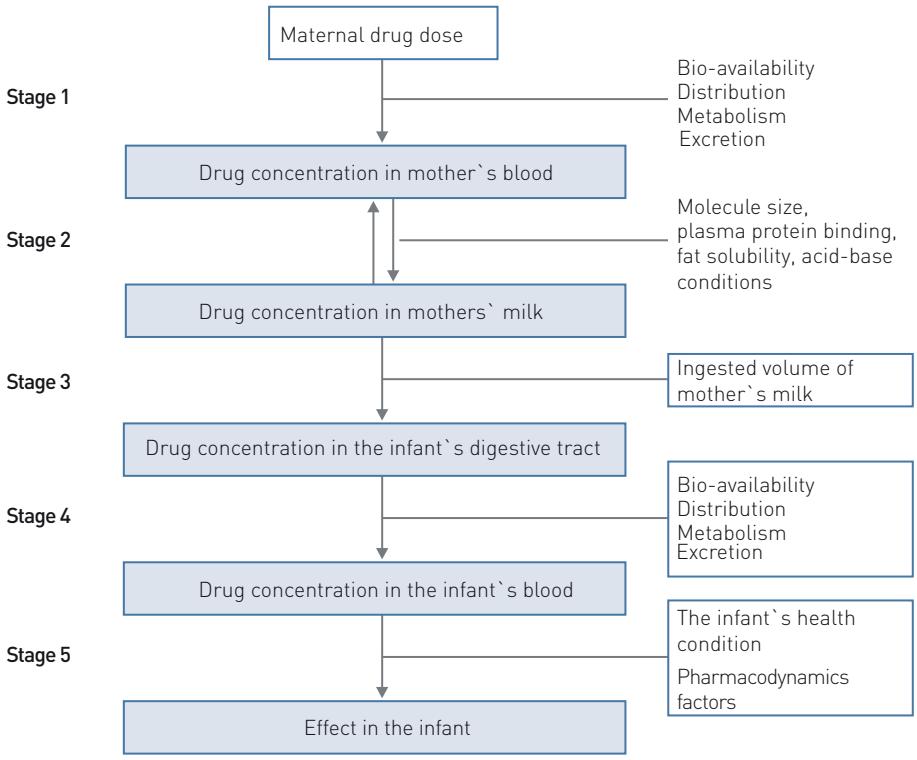

Figure 1: *Exposure to drugs in breast-fed infants by way of mother's milk (1–3)*

(unbound) drug. The drugs that most easily diffuse into mother's milk have a high concentration in maternal plasma, are fat-soluble, have a relatively low molecule weight (< 500) and a relatively low degree of protein binding in the plasma. For certain drugs, such as nitrofurantoin, cimetidine, ranitidine and aciclovir, the transfer to the mother's milk will take place via active transport through lipid membranes (1).

It is a common misconception that the drug remains in the milk, and that the women therefore should pump out and discard milk after having taken a medication that may affect her infant. The breast is not a reservoir where substances accumulate, like the urine bladder, but rather a compartment in dynamic equilibrium with maternal plasma. As the drug is gradually eliminated from the mother and the plasma concentration declines, the substance will diffuse from mother's milk back into the plasma. Pumping and discarding milk is therefore necessary only in exceptional cases, for example when the mother uses a contraindicated drug over a short period and needs to pump herself to maintain lactation and avoid breast engorgement.

The timing of breastfeeding seen in relation to the time of ingestion of the drug is a key determinant for the concentration of the drug in the milk at the time of breastfeeding. When the concentration reaches its peak level in the plasma it will, with a short delay, also reach its highest level in the milk. The concentration in the mother's milk and the amount of milk that the infant ingests will be decisive for the drug dose to the infant (stage 3). The drug must subsequently be absorbed from the infant's digestive tract before it can enter the bloodstream (stage 4). A high molecule weight restricts this absorption, and drugs which are proteins, such as insulin, will be degraded in the gastrointestinal tract. Furthermore, in infants older than 2–3 months, several drugs will be metabolised in the liver before they enter systemic circulation (first-pass metabolism). In newborns, on the other hand, and in premature infants in particular, this will occur to a lesser extent because of immature liver metabolism.

Finally, the drug must reach its effect site in sufficient amounts to exert a pharmacological effect in the infant (stage 5). Some drugs pass through all these stages, especially if the drug use continues over time, but in general, the amount reaching the infant's systemic circulation is so small that the substance will not produce any pharmacological effect.

Box 1

Estimation of the infant's theoretical dose and the infant's weight-adjusted relative dose

- The infant's theoretical dose (in mg/day) = the concentration in mother's milk (in mg/l) × 0.15 l/kg/day[1] × the infant's bodyweight (in kg).
- The infant's weight-adjusted relative dose (in per cent) = (the infant's dose (mg/kg bodyweight)/the mother's dose (mg/kg bodyweight)) × 100 %

[1] A fully breast-fed infant in general ingests approximately 150 ml of mother's milk per kilogram bodyweight per day.

Infant dose

If the drug concentration in the mother's milk is known, the infant's theoretical dosage can be estimated by multiplying this value with the volume of milk that the infant ingests (Box 1). To assess the risk of side effects, this dose can be compared to the recommended paediatric dosage (if known) for individuals of the same age/with the same bodyweight. For example, lamotrigine is transferred via mother's milk to a fully breast-fed infant in amounts corresponding to between 25 per cent and 50 per cent of the therapeutic paediatric dosage for infants, indicating that the risk of a pharmacological effect in the infant is present (1, 2).

In the literature, it is also common to report the infant's weight-adjusted relative dose, i.e. the dose that the infant ingests per kilogram bodyweight in relation to the mother's dose per kilogram bodyweight (Box 1). The transfer to mother's milk is regarded as minimal when the relative dose is below 2 per cent, small when the relative dose is 2–5 per cent, moderate when the relative dose is 5–10 per cent and high when the relative dose is more than 10 per cent. With relative doses above 10 per cent it is generally considered that a risk of pharmacological effects in the infant does exist (1, 2, 4). With lower doses, breastfeeding is in principle assumed to be safe – unless very toxic drugs such as cytostatics are involved.

Occurrence of side effects

Most data on side effects in breast-fed infants are derived from published case reports. Such reports are important since they can help generate hypotheses, but it is often difficult to determine whether there is a causal correlation between the symptoms in the infant and the drug exposure via the milk. Systematic prospective studies are therefore required. In a cohort study of breastfeeding women who were using a variety of drugs, the mothers were interviewed about possible side effects in their infants. The women reported suspected side effects in 11 of these 838 infants (5). The most frequently reported symptoms included pharmacologically plausible effects such as diarrhoea (antibiotics), drowsiness (opioids, hypnotics) and irritability (first-generation antihistamines). None of the cases required medical attention. These results indicate that the vast majority of cases of possible side effects are self-restricting and mild. There is also a prospective study of transfer of serotonin reuptake inhibitors to mother's milk, which included 26 exposed infants and 68 controls (6). No

increased risk of side effects was detected in these infants.

In a literature review published in 2003 in which side effects in 100 breast-fed infants were studied, two findings are especially relevant with regard to clinical practice. First, in nearly eight of ten cases, the infant was younger than two months and second, drugs that affect the central nervous system accounted for approximately half of all side effects (7).

Psychotropic drugs are the drug group that have been at the centre of attention among clinicians as well as researchers, and also the group that have been subject to the highest degree of uncertainty. Fortinguerra and colleagues reviewed the literature from 1967 to 2008 and identified 183 original contributions describing the use of psychotropic drugs during breastfeeding (8). They found that cases of side effects had been published for all groups of psychotropic drugs (except for psychostimulants, for which only one case report had been published) (8). Seen in relation to the number of mothers who are likely to have used such medications and breast-fed, the risk appears to be very low, however.

Breastfeeding is absolutely contraindicated for only a very few drugs (Table 1) (1, 2, 4, 9–21). Examples of such drugs include cytostatics, radiopharmaceuticals, iodine-based x-ray contrast fluids and gold compounds. Some drugs, such as cabergoline, are contraindicated because they may interfere with milk production or the process of lactation. It is far more common to advise caution with the use of a drug during breastfeeding on the basis of the pharmacological effects of the drug or its ability to pass into the mother's milk. Examples of such drugs include antipsychotics, opioids, benzodiazepines and certain antiepileptics (Table 1). The Journal of the Norwegian Medical Association has previously published articles on the use by breastfeeding women of analgesics (14), anaesthetics (15), antidepressants (16), antipsychotics (17, 18) and mood stabilisers (18).

In Box 2 we present questions that health workers should ask themselves on an individual basis to assess whether breastfeeding can be recommended or not. In some situations the problem can be solved by choosing a therapeutically equivalent alternative that is transferred to mother's milk to a lesser extent. In other situations this may not be possible. At the same time, it is essential to regard the exposure in a proper perspective: if the woman has used a drug during pregnancy she can most often continue using the drug while breastfeeding, since the infant's exposure will be far smaller than during pregnancy. This applies even though breast-fed infants themselves must metabolise and excrete drugs ingested via the milk. At the same time, in this situation the mother can choose to abstain from breastfeeding, thereby ceasing infant exposure. Recommendations to breast-feed or not should be based on a thorough risk/benefit assessment, in which the benefits of receiving mother's milk and the woman's own viewpoints should also be taken into account.

Factors affecting the risk of side effects

Several factors may increase the risk of side effects in breast-fed infants: high levels of the drug in the mother's milk, high toxicity, long-term drug therapy, infant health and not least the age of the infant.

Newborns, and premature infants in particular, eliminate many drugs at a considerably slower rate than older children and adults, because their liver and kidney functions are not yet fully developed (22). This applies both to drugs that are metabolised by the cytochrome P-450 system and drugs that

Box 2

Questions that can be used to clarify the risk/benefit relationship of drug use when the mother breastfeeds.

- About the infant:
  - How old is the infant?
  - Was the infant born prematurely?
  - Is the infant healthy?
  - Is the infant fully breast-fed?
- About the mother:
  - How necessary is this drug for the mother?
  - For how long will the mother use the drug?
  - How important is breastfeeding to her?
- About the drug:
  - Are there any alternative drugs that would be safer for the infant?
  - How large is the drug dose that the infant will ingest via mother's milk (if possible compared to a therapeutic dose for infants)?
  - Have any side effects in breast-fed infants been previously reported?

Table 1: Recommendations concerning breastfeeding and drugs – some examples (1, 2, 4, 9–21)

Recommendation	Can be used by breastfeeding mothers	Can be used by breastfeeding mothers	Can be used by breastfeeding mothers	To be used with caution in breastfeeding mothers. Single doses/sporadic use is regarded as safe	Breastfeeding must be assessed on an individual basis, if necessary with close follow-up of the infant.	Breastfeeding is contraindicated.
Examples	Antacids Insulin Eye drops	Antiasthmatics Most antibiotics Paracetamol Laxatives NSAIDs[1]	Antihistamines Most antidepressants Most antiepileptics Contraceptive pills containing gestagen/ mini-pills Thyroxine	Antipsychotics Benzodiazepines Beta-blockers Opioids	Ciclosporine Lamotrigine Lithium	Cytostatics Gold compounds Radiopharmaceuticals Iodine-based x-ray contrast fluids
Risk	No risk	No risk detected	Small risk	Small risk, provided that the drugs are used in single doses/ sporadically	Moderate risk	High risk
Knowledge base	The pharmacokinetics of these drugs indicate little or no systemic absorption from the infant's digestive tract.	These drugs have been used over long periods by breast-feeding mothers without any side effects in breast-fed infants being reported.	Studies show that the risk of side effects is low, or that the theoretical risk is low.	Studies show a small risk of side effects after repeated intake, or there is a theoretical risk of side effects in breast-fed infants because of accumulation.	Side effects have been reported, or the mechanism of action of these drugs indicates a risk of side effects.	Documented high risk in breast-fed infants, or the mechanism of action of these drugs indicates high toxicity.

[1] NSAIDs: non-steroid anti-inflammatory drugs

Table 2: Online resources for drug use and breastfeeding

Nationality	Website	Description
Norwegian	http://legemiddelhandboka.no	Norwegian pharmaceuticals handbook. The chapter Breastfeeding and drugs (G8) provides a general description of drug therapy with respect to breastfeeding women, and shows tables for drugs and groups of drugs sorted alphabetically and by active ingredient/group name (28)
Norwegian	www.relis.no	Regional drug information centres (RELIS). Contains a searchable database with responses to previous questions regarding drugs and breastfeeding (29).
Swedish	www.janusinfo.se	Janusinfo is a publicly funded Swedish website that provides information on drugs and breastfeeding, sorted alphabetically and by active ingredient and (Swedish) trade names (30)
British	www.ukmicentral.nhs.uk/drugpreg/qrg.htm	UK Midland Information Service contains lists of drug groups and their associated risk for breastfeeding women provided by British drug information centres (31)
American	www.toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT	Drugs and Lactation Database (LactMed) contains a searchable database of drugs/chemicals and breastfeeding from the US National Institute of Health (32)

undergo glucuronidation, and is reflected in elimination half-lives that vary with age. For example, the half-life of diazepam is approximately 80 hours in premature infants, approximately 30 hours in full-term newborns and 10–20 hours in infants after the newborn period (23). The renal function is not fully developed until the infant is 6–9 months old. Therefore, drugs with a high degree of renal elimination, such as lithium, have a considerably longer half-life in infants and in newborns in particular. In addition, seriously ill as well as premature infants will have a lower tolerance and will often be more sensitive than healthy children to the effects of drugs.

When using drugs with a long half-life, there will be a risk of accumulation in the infant if the ingested volume is larger than the infant's capacity for metabolising and excreting the drug. This could happen, for example, after continuous use of benzodiazepines, and drugs belonging to this group should therefore only be used sporadically in single doses in breastfeeding mothers.

On rare occasions, genetic factors will have an impact on the risk of side effects. Codeine is a clinically relevant example, e.g. when used after Caesarean sections or for painful vaginal tearing. A case of lethal morphine poisoning has been described in a 13 day-old breast-fed infant (24). The mother, who was an ultra-rapid metaboliser of the drug via the liver enzyme CYP2D6, had used codeine in amounts corresponding to two tablets of Paralgin Forte/Pinex Forte daily for somewhat less than two weeks. Blood samples from the infant showed a morphine concentration of 70 ng/ml, approximately 35 times the expected level. In comparison, the concentration in breast-fed infants is usually lower than 2 ng/ml. The mother's genotype resulted in increased production of morphine from codeine, and thereby in an abnormally high concentration in the mother's milk (measured to 87 ng/ml). Several cases of apnoea, drowsiness and bradycardia have been reported in infants exposed to codeine via mother's milk (21, 25). The use of codeine among breastfeeding mothers should therefore be restricted to a maximum of 2–3 days.

When side effects are suspected, analysis of the serum concentration of the drug in the mother as well as the infant, and possibly also in the milk, may be useful when assessing causality. A period without breastfeeding (when the mother pumps out and discards her milk) could be scheduled to observe whether the infant's symptoms disappear. If the symptoms return when breastfeeding is resumed this would give even stronger indications of causality. Suspected side effects should be reported to the nearest drug information centre (26).

How to reduce exposure

Occasionally it may be uncertain whether breastfeeding can be safely recommended when the mother uses drugs, for example during long-term treatment with some antiepileptics, antipsychotics and immunosuppressants (8, 11, 17–19). A possible solution in this situation could be to administer mixed nutrition, i.e. some mother's milk and some breast-milk substitute. With this compromise, the infant will be less exposed to the drug, and at the same time to some extent benefit from the valuable mother's milk.

For drugs with a short half-life, such as zolpidem, the risk of side effects can be reduced by breastfeeding at times when the drug concentration in the mother's milk is at its lowest level. This can be achieved by taking the drug immediately after breastfeeding, or immediately before the infant's longest sleep period.

If the woman is recommended to avoid breastfeeding while exposed to a drug, an estimation can be made of the time interval required before the drug is cleared from the milk or is present only in insignificant concentrations, so that breastfeeding can be resumed as quickly as possible. Information on the elimination half-lives of drugs can be found in the *Felleskatalogen* (27) and the *Norsk legemiddelhåndbok* (28). After a period equal to five times the half-life, for practical purposes all of the drug will have been eliminated from mother's plasma, and thereby also from her milk. For example, a woman who uses sumatriptan (with a half-life of approximately 1–1.5 hours) against migraine will be able to breastfeed after 5–8 hours.

When breastfeeding needs to be individually adapted to reduce the infant's exposure to drugs, this will often require an extra effort from the responsible doctor in terms of providing information to the mother and performing follow-ups of the mother and infant. One example is when the mother uses lithium and has a strong desire to breastfeed; in some cases this may be possible, even though it is generally discouraged. This solution presupposes that the mother receives thorough information and that the infant is monitored closely both clinically and by laboratory testing (18).

Information sources

Norsk legemiddelhåndbok contains a separate chapter on drugs and breastfeeding. Here, each individual compound is assessed in terms of its safety of use during periods of breastfeeding (2). Each drug is classified in one of six risk categories, which may be of help for an individual risk/benefit assessment. Side effects that may occur in breastfed infants and of which breastfeeding mothers should be aware are also described. Information pertaining to infant safety in breastfeeding is also found in national therapy guidelines with regard to several groups of drugs, such as antiepileptics (19), antibiotics (20) and analgesics (21).

The descriptions in the product monograph *Felleskatalogen* will rarely be a good source of information to breastfeeding mothers, because of the legal provisos that the manufacturers tend to include in their texts. As far as international literature is concerned, we can especially recommend Hale's *Medications and mother's milk* (1). Most questions pertaining to the safety of breastfeeding and the use of drugs can be answered with the aid of this manual. Several good online resources are also available (Table 2) (28–32).

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