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Drug excretion into breast milk—Overview

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Abstract

Breastfeeding is the optimal form of infant feeding for the first months of an infant's life, and the majority of healthy women initiate breastfeeding after the birth of their infant. However, women on medication may default to formula feeding or not taking their drug therapy for fear of exposing their infant to the medication through the breast milk. Although the majority of medications are considered to be compatible with breastfeeding, cases of significant infant toxicity exist, suggesting a case by case risk assessment to be made before the mother initiates breastfeeding or drug therapy. Unfortunately, current clinical risk assessment is often compromised by the paucity of data, as studies in breastfeeding women and their infants are ethically difficult to conduct. Circumventing the ethical constraints, approaches have been proposed to estimate drug excretion into milk from physicochemical characteristics of the drug, which diffuses through the mammary gland epithelia. However, as our understanding on drug transfer mechanisms increases, it has become abundantly clear that carrier-mediated processes are involved with excretion of a number of drugs into milk. This article provides an overview of the benefits of breastfeeding, the effect of medication use during breastfeeding on maternal decisions and infant health, and factors determining infant exposure to medication through the breast milk.

Keywords: Adherence; Breastfeeding; Drug effect; Drug therapy; Drug transfer; Human milk; Milk production; Neonate

Contents

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1. Introduction

Milk production and nursing constitutes the biological norm for mammals. Breast milk provides necessary nutrients to the infant for the first 6 months of life [1]. Additionally, numerous studies have associated breastfeeding with potential medical, and social benefits, which include decreased mortality and morbidity in infants from infectious and other diseases, potential advantages in infants' cognitive development, and decreased incidence of cancer and osteoporosis in the mothers. Thus, current guidelines by professional organizations such as the American Academy of Pediatrics and the Canadian Pediatric Society recommend that infants be exclusively breastfed for at least the first 6 months of life.

Following a decline in the 1950s, breastfeeding has regained popularity, reaching stable initiation rates of 60–90% in most industrialized countries [2,3]. While breastfeeding is being strongly promoted, recent medical progress of pharmacotherapy has resulted in a dilemma. Namely, almost all lactating women receive some medications immediately postpartum and during breastfeeding [4,5]. Consequently, there is an increased likelihood for newborns, at least in industrialized countries, to be breastfed by mothers on medications. Needless to say, not only drugs, but also environmental chemicals and non-medicinal substances constitute other important groups of compounds potentially contaminating human milk. However, our knowledge of drug transfer in the mammary gland and its clinical consequences are limited at best, thus creating a great deal of confusion among patients and health care professionals. This is exemplified by decreased adherence to maternal drug therapy during breastfeeding. Clearly, it is of utmost importance to fully reveal and understand the biological mechanisms, pharmacological principles, and clinical consequences of drug excretion into breast milk.

Studies have indicated that the mammary gland has various carrier-mediated systems, by which drugs are transported into milk. This implies that manipulation of these systems, pharmacological or otherwise, may enable us to control excretion of drugs into milk. Our knowledge on this subject will not only improve clinical management of lactating women on medications, but also present an intriguing possibility of an innovative mode of drug delivery to nursing infants who benefit from therapeutic concentrations of the drug in milk.

2. Epidemiology

2.1. Breastfeeding initiation rate

Since the 1970s, the percentage of women choosing to breastfeed over formula feed has been on the increase [2,3]. This may be due to increased awareness by the general public, prompted by research, and recommendations by professional organizations (e.g., American Academy of Pediatrics, Canadian Pediatric Society, UNICEF).

Although approximately 96% of women are physiologically able to breastfeed under normal conditions [6], a 1994–1995 survey conducted by Health Canada found the national breastfeeding initiation rate to be 73%. The 1996–1997 National Population Health Survey found that 79% of Canadian women breastfed their last child [7]. In 1995 in the United States, about 60% of women were breastfeeding at the time of hospital discharge [8].

The decision to initiate breastfeeding is positively associated with socioeconomic status, maternal age, and education, as well as spousal support and encouragement [9–11]. However, when a nursing woman requires medication, the decision on infant feeding method may become very different. Even if the drug is considered safe for breastfeeding dyads,

their decision on the feeding method is often influenced heavily by overcautious advice.

2.2. Medication use of nursing women

Approximately 90% of women take some form of medication during their first week postpartum [4,5] Studies have shown breastfeeding initiation and duration to decrease when women require medication. Furthermore, this is observed not only for medications known to be contraindicated during breastfeeding, but also drugs proven to be compatible. For example, 22% of lactating women requiring antibiotics, which are considered safe during breastfeeding, either stopped breastfeeding or did not begin therapy [12]. Moreover, women were less likely to take medication as a result of physicians' negative advice against breastfeeding during the therapy, even if the available evidence-based information had established safety [12]. Similarly, breastfeeding initiation rates are lower in women on chronic medications, even if the current recommendation is in favor of continuation of breastfeeding during the therapy [13,14]. Clearly, of utmost importance are both an increased research effort in this field and effective knowledge transfer into clinical practice, so that postpartum women and the family can make a well-informed decision.

3. Benefits of breastfeeding

3.1. Infant

The mortality and morbidity of infants in developing countries is dramatically reduced (by as much as 300 deaths per 1000 live births) if they are breast-fed [2]. While this is mainly a result of poor sanitary conditions associated with bottle feeding, industrialized societies show similar trends [2]; for example, in Sheffield, UK, breastfeeding accounted for an estimated 24% reduction in the infant mortality rate [15].

The health benefits of breastfeeding encompass not only reductions in mortality, but also a decrease in morbidity from acute infectious disease such as *Campylobacter* enteritis [16]. There are reports suggesting that immunologically-mediated abnormalities are also decreased [17] in later life if an infant is breastfed [17,18]; for example, formula feeding has been estimated to account for 2–26% of insulin-dependent diabetes [17].

It is widely accepted that breastfed infants have a lower risk of developing necrotizing enterocolitis, gastrointestinal ailments, otitis media, the sudden infant death syndrome (SIDS), lower respiratory tract infections, respiratory syncytial virus infection, insulin dependent diabetes mellitus, and allergies (Table 1) [16,17,19–25]. Studies have shown that benefits increase with the duration and exclusivity of breastfeeding [26,27].

Compared to formula fed infants, breastfed infants score higher on tests measuring neurodevelopment [28–32]. Despite the methodological difficulties of being unable to randomize from ethical constraints, studies continue to emerge, indicating that the statistical significance of higher cognitive function of breastfed children remains even after adjusting the potential confounders. A recent study further suggests that the effect lasts well into adulthood [32]. Overall, the robust beneficial effects of breastfeeding (or breast milk feeding) on the offspring's cognitive function are in the range of about 6–10 IQ points, which approximates $1/2 - 2/3$ of a standard deviation. The societal implications of a population with slightly higher neurodevelopmental scores are immeasurable. Because breastfeeding is associated with factors such as higher parental education and socioeconomic status, it is crucial to control for these confounders. These potential beneficial effects on the infant's cognitive function have been an issue of

Table 1
Medical benefits of breastfeeding [16–25]

Illness	Estimated risk reduction in breastfed infants (vs. formula fed infants)
Gastrointestinal/diarrhea	1/3–1/2
Otitis media	1/4–1/3
Urinary tract infection	1/5
Bacterial meningitis	1/16–1/4
Necrotizing enterocolitis	1/10
Respiratory syncytial virus	1/2
Type II diabetes	1/3

controversy, because the study methods are under severe constraints as randomization is unethical.

3.2. Mother

The nursing women also benefit from breastfeeding. Breastfeeding increases maternal levels of oxytocin, thus resulting in decreased postpartum bleeding and quicker uterine involution. The act of breastfeeding is associated with increased maternal-infant bonding, and maternal sense of fulfillment and self-worth. Increased oxytocin and prolactin in the mother induces feelings of relaxation and well-being. Women who breastfeed benefit by returning to their pre-pregnancy weight more rapidly than those who choose to formula feed [33]. Increased child spacing (due to delayed resumption of ovulation) [34,35], and reduced risk of ovarian and pre-menopausal breast cancer are also benefits of breastfeeding. Finally, although bone density is decreased during the breastfeeding period, subsequent bone remineralization results in decreased incidence of hip fractures in the post-menopausal period [36].

3.3. Society (economic benefits)

The direct cost of formula feeding to the family is significantly greater than the cost of breastfeeding. During the first 6 weeks postpartum, the caloric requirements of a breastfeeding mother are equivalent to that of a nonlactating woman. Although after this time period, breastfeeding women require an additional 200 kcal/day, cost for food is approximately 1/2 that required to purchase formula [37]. In 1993, it was estimated that breastfeeding saves $>$ $885 US in formula purchases during the first year of life [38]. This is not taking into account costs for bottles, teats, bottle liners, breast pump, nursing pads, and other hidden costs (for both formula and breastfeeding). The association between returning to work and breastfeeding duration has been shown to result in productivity gains in women who choose to formula feed [39,40]. However, women can still pump and store their breastmilk to be provided to their infant while they are working.

As outlined so far, breastfed infants have a lower risk for developing certain illnesses. Consequently, utilization of health resources is decreased in this population, resulting in savings to the health care system. Drane (1997) estimated that $11.5 million could be saved each year in Australia if the breastfeeding prevalence at 3 months was increased from 60% to 80% [41]. Ball and Wright (1999) estimated that by breastfeeding, US$331–475 per infant could be saved in health care costs during the first year of life [42].

4. Adverse outcomes of maternal drug therapy during lactation

If maternal medication use is necessary during lactation, breastfeeding women and health professionals are mainly concerned about exposure of the infant to the drug and how this may affect infant health and development both in a short and long term. Some medications may decrease milk production, and this is viewed as an adverse outcome as well. In addition, as discussed in the previous section, breastfeeding may reduce maternal adherence to drug therapy. Similarly, if the drug considered safe during breastfeeding is for chronic condition, decision on the feeding may be affected. These three factors will be discussed in the following section.

4.1. Infants

Although the majority of medications taken by lactating women have been shown not to cause overt adverse events in the suckling infant, there is little epidemiological data about the probability of the adverse effects of maternal drugs on breast-fed infants. Follow-up data on 838 breast-fed infants exposed to various drugs taken by their mothers showed that about one in ten nursing mothers reported some changes in conditions of their infants, which coincided with their drug treatment [43]. Importantly, none of these needed medical attention [43]. On the other hand, there have been many case reports of clinically significant toxicity in breast-fed infants from some medications used by mothers (Table 2) [43–58].

There is a case report of significant beta-blockade in a neonate breastfed by a woman on atenolol after delivery [45]. Atenolol, a beta-blocking agent used

Table 2
Maternal drugs with reported toxicity in breast-fed infants

Drug*	Toxicity	Ref.
Atenolol	Excessive β-blockade	Schmimmel [45]
Caffeine	Irritability, poor sleeping	Hill [46]
Cocaine	Marked irritability	Chasnoff [47]
Ergotamine	Vomiting/diarrhea	Fominal [48]
Doxepin	Respiratory depression,	Matheson [52]
	Poor suck and swallow, hypotonia, vomiting	Frey [51]
Fluoxetine	Irritability	Lester [49]
	Poor weight gain	Chambers [50]
Lithium	Near therapeutic serum levels in the infants	Tunnessen [53]
		Schou [54]
Nicotine	Shock, vomiting	Bisdom [55]
Phenobarbital	Sedation	Tyson [56]
Salicylate	Metabolic acidosis	Clark [57]
Theophylline	Irritability	Yurchak [58]

*Including substance of abuse.

for control of hypertension, is mainly eliminated through glomerular filtration. This medication is also known to be accumulated in milk (milk-to-plasma ratio of about 2). In addition to its relatively high excretion into milk, immaturity of renal function of the infant was probably one of the contributing factors to the toxicity in this case. Also, meperidine administered to mothers after delivery, and presumably excreted into milk, reportedly caused neurobehavioral depression in the breastfed infants, compared to morphine [59]. Thus, although some drugs are taken safely by lactating women, some result in significant exposures and toxicity in the infants.

Most recommendations on the safety of medications during lactation are based on theoretical risks, case reports, or single case studies that measured breast milk or infant serum drug levels. Although a handful of prospective, cohort studies exist, there is an overall lack of published information confirming risks of adverse effects to the infants

Whereas pharmaceutical companies often indicate that their products are not recommended for use during lactation, current opinion now stands that no medication is an absolute contraindication during breastfeeding. Although the American Academy of Pediatrics categorized several medications as contraindicated in their 1983–1994 reports on the transfer of medications into breast milk [60], these lists were deleted in their 2001 report [61]. Instead, these medications were recategorized as agents that should be used with caution. Thus, contraindications should be assessed on a per patient basis, with the benefits and risks to both the mother and infant weighed. The presence of adverse events reported in the literature, or the theoretical risks of adverse events does not automatically suggest contraindication, although a cautious approach may be required (e.g. monitoring the infant for physical/behavioural changes).

Risk assessment of maternal drug treatment during breastfeeding is further complicated by lack of data on long-term adverse outcomes in the infants. Such effects may include behavioral and subtle cognitive changes that may become overt only later in the infant's life. This is a concern, especially for psychoactive medications, even without apparent immediate clinical effects. Without the data, it is impossible to interpret and assess clinical significance of any amounts of drug excreted into milk, and ingested by the infant.

4.2. Milk production

A small group of medications has been shown to have an adverse effect on milk production. Of these, breastfeeding women are most commonly exposed to oral contraceptives containing estrogen derivatives. Current levels of estrogen derivatives found in combined oral contraceptives formulations reduce breastmilk production by 20–30% [62–65]. In the first few weeks postpartum, a decline by as much as

40% has been reported [62,66]. Whether this has a clinically significant impact on the growth and development of the nursed infant is unclear. However, breastfeeding duration has been shown to be compromised in women on estrogen-containing contraceptives [67,68]. Given the known benefits of breastfeeding, infants who are weaned off breast milk prematurely may not acquire the full benefits associated with breastfeeding. Progestin-only contraceptives have little to no adverse effects on breast milk production [65,69].

Other medications that have been reported to reduce milk production include bromocriptine, ergotamine, and bendroflumethiazide [70]. Metoclopramide and domperidone, on the other hand, increases milk supply. Especially, domperidone has been shown to effectively sustain milk supply in mothers of preterm babies, who had difficulty in maintaining milk supply [71].

4.3. Maternal adherence to drug therapy

Women seeking information on the safety of her medication to the breastfed infant may turn to numerous sources. The internet, media, family, friends, drug manufacturers, and health care providers may all be consulted. Often, the information received may be conflicting, as it may not be evidence-based. Thus, it is common for opinions and perceptions to be formed based on misinformation.

Maternal adherence to drug therapy may be compromised if there is a perception that exposure to the medication through the breast milk may be harmful to the nursed infant. This was shown in antibiotics therapy during breastfeeding. Twenty two percent of lactating women requiring antibiotics either stopped breastfeeding or did not begin therapy [12]. This was especially evident if women were given equivocal advice from health professionals with regard to choice of feeding during the drug therapy.

When chronic medications are required by lactating women (e.g. epilepsy, and hyperthyroidism), it may be more difficult for a woman to discontinue therapy. In these cases, women are more likely (when compared to acute antibiotics therapy) to continue medication and default to formula feeding. Studies in Canada indicated that breastfeeding initiation rates are approximately 50% for those receiving carbamazepine [13,72] or propylthiouracil [14], both of which are compatible with breastfeeding, compared to 80–90% for the control women. Unfortunately, incorrect advice from physicians has a significant influence on the women's decision not to breastfeed during drug therapy that is considered compatible with nursing [13,14]. In the area of mental health, such as depression, this over-cautious approach commonly results in more significant consequences; the postpartum women tend to discontinue the medication in order to breastfeed, which can lead to significant morbidity and mortality to both the mother and infant [73].

5. Infant exposure to drugs in milk

5.1. Determinants of infant drug exposure

The ratio between drug concentrations in milk and maternal plasma/serum is called the milk-to-plasma/serum drug concentration ratio (MP or MS ratio). This is a time-dependent parameter, influenced by factors such as maternal pharmacokinetics and compositional changes of milk. It was proposed that the ratio can be predicted from the physicochemical characteristics of the drug that is mainly transferred into milk by passive diffusion [74,75].

'Exposure Index' has been proposed as a concept linking MP ratio, milk intake, and the infant drug clearance to a time-averaged drug exposure level of the breastfed infant:

$$\text{Exposure Index (\%)} = 100 \times \text{MP ratio} \times \text{A}/\text{Infant Drug Clearance}$$

where A is milk intake (150 ml/kg/day = 0.1 ml/kg/min), and Clearance is expressed as ml/kg/min [44,76]. This parameter is conceptually equivalent to the infant dose of the drug in milk that is expressed as percentage of the infant therapeutic dose (i.e., established or theoretical). Alternatively, it can be viewed as a mean steady-state serum drug concentration of the breastfed infant (which is achieved after exposure to the drug in milk) expressed as a percentage of the corresponding therapeutic serum level (i.e., established or theoretical).

Because of its hyperbolic relation to infant drug

clearance, the Exposure Index becomes very high at a low clearance (e.g., <1 ml/kg/min) (Fig. 1) [44,76]. Also, MP ratio may have substantial impact on the exposure level, if the infant drug clearance is sufficiently low. Hence, both the mechanisms governing drug transfer into milk, and infant pharmacokinetics including drug clearance are important determinants of the exposure levels. In the final chapter of this issue, McNamara further expands and refines the concept of Exposure Index, providing a rigorous theoretical framework for risk assessment.

5.2. Mechanisms of drug transfer into milk

Drug transfer into breast milk is determined by factors such as ionization, plasma protein binding, molecular weight, lipophilicity of the drug, and its pharmacokinetics in the mother. In general, low plasma protein binding, low molecular weight, high lipophilicity, and cationic drugs favor increased excretion of the drug into milk. Biochemical characteristics of milk including lower pH and higher lipid contents compared to plasma contribute to this phenomenon. In addition, milk compositions change over several postpartum weeks from colostrum, transitional, to mature milk, and within a feeding period between foremilk and hindmilk. These factors contribute to the time- and phase-dependent variation of drug excretion into milk. Another source of variation is the possible presence of carrier-mediated drug transport mechanisms.

Although excretion of many drugs can be explained with a passive diffusion model [74], there are exceptions. For example, excretion of organic cations such as cimetidine [77,78] and ranitidine [78] into milk of rats is more than expected from simple diffusion and ion trapping. An in vivo human study by the same group has also shown that accumulation of cimetidine in milk is significantly higher than expected from passive diffusion [79]. These studies suggested that the mammary gland has a carrier-mediated transport system(s) for organic cations.

Benzylpenicillin was a significant ‘outlier’ among the acidic drugs investigated by the passive diffusion model (its excretion is more than expected). Indeed, an in vivo animal study showed that the transport of benzylpenicillin across the mammary gland of goats and cows is reduced by concomitantly given probenecid, suggesting a presence of a carrier-mediated system for the drug [80]. The transfer of an acidic antibiotic, nitrofurantoin, into rat’s milk is nearly 75-fold higher than predicted from passive diffusion [81]. In humans, a 20-fold higher excretion was observed when compared to levels predicted due to passive diffusion [82]. Dipyridamole effectively inhibits the transfer of nitrofurantoin into rat’s milk [83]. However, the molecular identity of the dipyridamole-sensitive nitrofurantoin transporter remains to be determined.

In vivo data has been accumulated, indicating existence of carrier-mediated systems for certain drugs. As discussed later in this issue, the molecular

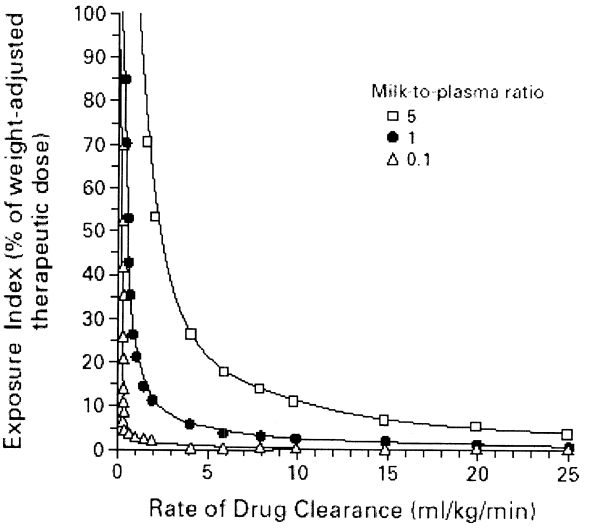

Fig. 1. Relation between the level of exposure of an infant to the drug excreted in breast milk and the rate of clearance of the drug by the infant. According to the ration of the drug concentration in the milk to the drug concentration in maternal plasma. The relation can be expressed by the following equation: the exposure index (expressed as a percentage of the weight-adjusted therapeutic dose in infants) $=[A\times(\text{milk-to-plasma ratio})/CL_i]\times 100$, where A is the average milk intake (e.g., 150 ml per kilogram of body weight per day, or 0.1 ml per kg per min), the milk-to-plasma ratio is the ratio of the drug concentration in breast milk to that in maternal plasma, and CL_i is the rate of drug clearance by the infant (expressed in ml per kg per min). Drugs with low rates of clearance are likely to result in a substantial degree of exposure ($>10\%$ of the weight-adjusted therapeutic dose). In addition, changes in the milk-to-plasma ratio influence the level of exposure, especially if the rate of clearance of the drug is low. Reprinted from Ito [44], and Ito and Koren [73], with permission of the publishers.

identity and functional significance of these mechanisms have also begun to emerge. For example, mRNA expression of transporters such as certain organic cation and anion transporters, nucleoside transporters, and multidrug resistance associated proteins have been reported [84–86]. It seems fair to assume that drug transfer into milk hinges on a dynamic balance between various drug transporters in addition to diffusion processes.

5.3. Development of drug elimination systems in the infant

At a given intake and a concentration of drug in milk, lower clearance causes higher drug exposure levels of the breastfed infant. Overall, clearance values are lower in neonates and young infants due to immaturity of drug elimination systems, although variations exist between drugs in their development patterns of clearance because the ontogeny of each elimination system has its own time-profile of development.

Renal excretion of drugs depends on glomerular filtration, and net tubular secretion. Glomerular filtration rate (GFR) begins to increase significantly at around 34 weeks gestation [87]. Yet, the GFR of full-term neonates at birth is as low as 25% of the adult level on a body weight basis [87,88]. Increase in the postnatal GFR depends on postconceptional age, and adult values are achieved by 3–5 months of age [88,89]. Tubular function appears to mature at a slower rate than GFR. For example, maximum tubular transport of para-aminohippurate reaches an adult level by 30 weeks of life, showing a 10-fold increase from birth [89]. This is exemplified by prolonged elimination half-lives of furosemide in neonates, which is secreted through the para-aminohippurate pathway [90–92].

Developmental profiles differ among drug metabolizing enzyme families. Within a family, individual enzymes often show specific developmental patterns affecting the ontogeny of drug clearance. Overlapping substrate specificity and genetic polymorphisms add another level of complexity to the resultant phenotypes of drug biotransformation in neonates and infants.

Cytochrome P450 (CYP) enzymes constitute an important group of Phase I drug metabolizing enzymes. CYP3A7, an enzyme that mediates the metabolism of endogenous steroids and xenobiotics, is expressed mainly in fetal liver and decreases in its expression postnatally. After birth, CYP3A4 replaces CYP3A7, reaching 40% of the adult level after 1 month [93]. In human liver, CYP1A2 is the last drug-metabolizing CYP to emerge over the first 3 postnatal months [94]. On the other hand, CYP2D6 and 2E1 expressions in liver increases rapidly within hours of birth [95,96].

Not only drug clearance, but also development of intestinal drug elimination and absorption processes is important, as drug in milk is subjected to absorption and first-pass elimination processes by the gastrointestinal tract and liver of the infant. In rats, intestinal CYP3A expression does not dramatically increase before weaning [97]. Intestinal expression of *P*-glycoprotein, a drug-efflux pump with broad substrate specificity, also increases after birth in mice [98]. In humans, data on the development of intestinal CYP enzymes and *P*-glycoprotein are non-existent.

6. Summary

Benefits of breastfeeding include anti-infective properties, cognitive function enhancing, and immunomodulating effects in the infants. In addition, maternal and societal benefits are considered tangible. While breastfeeding must be encouraged, maternal drug treatments pose a difficult question. Facing uncertainty to the consequences of infant exposure to drugs in milk, women may compromise their own indispensable pharmacotherapy, or become overcautious by choosing formula. The uncertainty about infant safety stems not only from ignorance of the existing data by health professionals, but also the lack of clear understanding on how the drug is excreted into milk, and what the clinical significance is. Despite research effort, key questions remain largely unanswered.

Transporter gene transcripts have been identified in the human mammary gland during lactating and non-lactating stages. Although in vivo evidence indicates the presence of carrier-mediated systems in the mammary gland, protein expression and functional significance of the transporters in drug excre-

tion into human milk remains to be elucidated. The knowledge on drug transfer mechanisms in the mammary gland will also open a door to the intriguing possibility of novel approach of drug delivery to a nursing infant. In parallel to elucidation of drug transfer mechanisms, the ontogeny of drug excretion and biotransformation processes in the infant needs to be fully characterized. Finally these data must be accompanied by the knowledge of the clinical consequences of infant exposure to a given drug in milk; i.e., potential drug effects for both short- and long-term. Although it is true that most drugs are excreted into milk at only a low concentration, making dose-dependent, pharmacological effects on the infant unlikely, definite evidence of the lack of short- and long-term effects needs to be clearly presented.

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