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A novel index for expressing exposure of the infant to drugs in breast milk

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1 We present a novel index for expressing the exposure of the infant to drugs in breast milk, which unifies two independent factors: a pharmacokinetic parameter, drug clearance, and a physicochemical parameter, i.e. milk-to-maternal plasma drug concentration ratio (M/P ratio).

2 During breast-feeding by a woman receiving therapeutic doses of a drug at steady state this index is given by:

$$\text{Exposure index} = A \times (\text{M/P ratio})/CL_I$$

where A is a coefficient (10 ml kg^{-1} min^{-1}) and CL_I is drug clearance in the infant (ml kg^{-1} min^{-1}).

3 This equation indicates a hyperbolic relationship between drug clearance and the exposure level of the breast-fed infant at a given M/P ratio of drug, emphasizing the importance of drug clearance as a determinant of infant exposure.

Keywords breast-feeding human milk clearance drug infant

Introduction

Drug excretion in milk has been a matter of concern for nursing women on medications as well as for health professionals caring for them. Whereas formula feeding is available as an alternative, increasing evidence of the benefits of breast-feeding makes it necessary for physicians to assess the risk/benefit in infants breast-fed by women on medications.

To determine the magnitude of risk, it is necessary to know the amount of drug excreted into milk. Most drugs are excreted into milk by passive diffusion. Accordingly, drug concentration in milk is directly proportional to the corresponding concentration in maternal plasma. The milk-to-maternal plasma drug concentration ratio (M/P ratio) is used as an index of the extent of drug excretion in milk. Several physicochemical properties of the drug (e.g. protein binding, ionization, and lipophilicity) have been identified as major determinants of M/P ratios [1–3].

However, the M/P ratio is often overly interpreted, if not misinterpreted. Specifically, drugs with lower M/P ratios are said to be safe for the infant during breast-feeding, whereas those with higher M/P ratios indicate concern. This is not always correct because the clearance of the drug by the infant also has to be taken into account. For example, if the infant needs a high dose of drug to achieve a plasma concentration consistent with a clinical effect (high clearance drugs), an M/P ratio of 10 might be insufficient to cause the level of exposure in the infant. On the other hand, if a small amount of drug is needed to achieve a plasma concentration consistent with an effect (low clearance drugs), an M/P ratio of 0.1 might result in sufficient accumulation. Thus, drug clearance is an important factor in determining the exposure level in the infant.

Although the role of drug clearance in this context has been stressed repeatedly [2, 4], the concept has not been presented concisely. We describe a simple equation for expressing the exposure of the infant to a drug in breast milk, which encompasses the concepts of both clearance and M/P ratio. This equation emphasizes the preference for using high-clearance drugs during breast-feeding, and leads to a simple estimate of infant drug exposure when there are no experimental data on drug concentrations in milk.

Methods

The infant exposure level was defined as the dose an infant would ingest with milk, expressed as a percentage of the infant's therapeutic dose per body weight.

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This is designated as the Exposure Index (EI). An EI of 100% equals therapeutic exposure.

The following assumptions were made: 1) the mother receives a standard therapeutic dose; 2) the mother achieves a therapeutic plasma drug concentration at steady-state; and 3) the infant is breast-fed constantly by the mother.

The daily dose of drug in milk an infant would ingest per kg body weight (D_{milk}) is given by:

$$D_{milk} = (\text{M/P ratio}) \times C_{ss} \times \text{Daily milk intake}$$

where C_{ss} is the maternal plasma drug concentration at steady state. Thus, the Exposure Index (EI) is derived by comparing D_{milk} to the infant's daily therapeutic dose (D_I) as follows:

$$\begin{aligned} EI &= D_{milk} \times 100/D_I \\ &= [(\text{M/P ratio}) \times C_{ss} \times \text{Daily milk intake} \times 100]/D_I \end{aligned}$$

D_I and drug clearance in the infant (CL_I) are related by:

$$CL_I = F \times D_I/C_{ss,I}$$

F is bioavailability, and $C_{ss,I}$ is the steady-state plasma drug concentrations in the infant receiving a therapeutic dose directly by mouth. Therefore, when F equals unity:

$$EI = [(\text{M/P ratio}) \times C_{ss} \times \text{Daily milk intake} \times 100]/(C_{ss,I} \times CL_I)$$

If it is assumed that $C_{ss} = C_{ss,I}$, and that milk intake is 150 ml kg^{-1} day^{-1} (about 0.1 ml kg^{-1} min^{-1}), then:

$$\begin{aligned} EI &= (\text{M/P ratio}) \times (\text{Daily milk intake} \times 100)/CL_I \\ &= (\text{M/P ratio}) \times A/CL_I \qquad (1) \end{aligned}$$

where the coefficient A is 10 ml kg^{-1} min^{-1} (0.1 ml kg^{-1} min^{-1} × 100 = 10 ml kg^{-1} min^{-1}), and CL_I is expressed as ml kg^{-1} min^{-1}. Note that equation (1) may underestimate infant exposure when $C_{ss} >> C_{ss,I}$ (e.g. due to a significant difference in pharmacodynamics).

Because data in infants on drug clearance and therapeutic doses are often lacking, the adult therapeutic dose (D_A) or clearance (CL_A) may be used. This exposure index is designated EI_A and is given by:

$$EI_A = D_{milk} \times 100/D_A \qquad (2)$$

$$= (\text{M/P ratio}) \times A/CL_A \qquad (3)$$

where bioavailability is assumed to be unity.

A correction factor (α) may be used to relate EI to EI_A:

$$EI = \alpha \times EI_A \qquad (4)$$

Equation (1) was used to calculate corresponding EI values for a range of theoretical CL_I values and M/P ratios of 0.1, 1, and 5. In addition, we retrieved experimentally derived EI_A [4] and mean CL_A values [6, 8] of 86 drugs from the literature (84 drugs from [6]; and 2 from [8]). The experimentally derived EI_A values were calculated as '% maternal' doses by Atkinson *et al.* [4] using an expression identical to equation (2), where D_{milk} was the product of peak drug concentrations measured in milk, milk intake was 150 ml kg^{-1} day^{-1}, and D_A was standardized for a maternal weight of 60 kg. Where two or more EI_A values or a range of EI_A values had been cited for a single drug [4], the average of the highest and lowest values was used in our analysis. For those drugs showing saturable kinetics C_{ss}, and hence CL_A, were estimated from a Michaelis-Menten function [7]; C_{ss} values of phenytoin, ethanol, and probenecid were assumed to be 10 μg ml^{-1}, 100 mg dl^{-1}, and 100 μg ml^{-1}, respectively. Creatinine clearance was assumed to be 2 ml kg^{-1} min^{-1} when CL_A was expressed with respect to creatinine clearance. When clearance values had been cited for slow and fast metabolizers [6], those of the former were used. For both the theoretical and experimental data, plots of exposure index *vs* clearance were constructed.

Equations (1) and (3) imply that the exposure index for a drug may be predicted from a theoretical M/P ratio and a population average value of clearance, when there are no experimental data on drug concentrations in milk or M/P ratios. To assess the prediction of EI_A by equation (3), linear regression of the predicted EI_A values on the aforementioned experimentally derived EI_A values [4] was examined. The predicted EI_A values were calculated by us from theoretical M/P ratios [5] and population average CL_A values [6, 8]. Thirty-three drugs available for both the predicted and experimentally determined EI_A values were included in this analysis.

The theoretical M/P ratios derived by Atkinson *et al.* [5] were based on physicochemical properties namely protein binding, ionization, and lipophilicity. (In their study [5], the theoretical values of M/P ratio were derived in two ways, and designated as either 'M/P'_{phase}' or 'M/P_{phase}'. We used mostly the former values; the latter being used in default of the former.) Average CL_A values were retrieved from the literature [6, 8] as described before. When standard deviations of mean values of CL_A were provided, we also calculated EI_A with the lower (i.e. mean − s.d.), and the higher CL_A (mean + s.d.) to represent a range of predicted EI_A values.

Results

The hyperbolic relationship between exposure index and drug clearance is illustrated in Figure 1a and b for theoretical EI and experimental EI_A data, respectively. The plots indicate that infant exposure in milk to drugs with clearance values greater than 5 ml min^{-1} kg^{-1} is likely to be low (EI and EI_A < 10%).

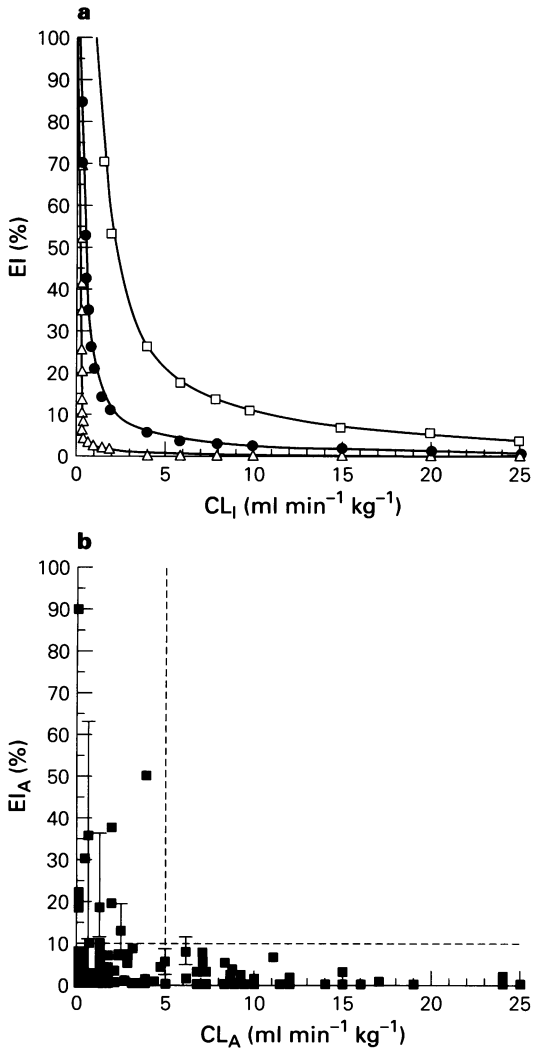

Figure 1 Relationship between clearance and infant exposures to drug in breast milk. a) Theoretical relationship between infant exposure (EI) and drug clearance in the infant (CL_I) at three different milk-to-maternal plasma drug concentration ratios (M/P ratio) (□ M/P = 5; ● M/P = 1; △ M/P = 0.1): EI = A × (M/P ratio)/CL_I, where coefficient A is 10 ml kg^{-1} min^{-1} and CL_I is expressed as ml kg^{-1} min^{-1} (see text: Equation 1). Note that changes in M/P ratio can result in substantial effects on infant exposure if the clearance of the drug is sufficiently low. b) Relationship between the index (EI_A) derived experimentally from measured peak drug concentration in milk and drug clearance in adults (CL_A) of 86 drugs. Note that all drugs with EI_A of greater than 10% (horizontal dotted line) have clearances lower than 5 ml kg^{-1} min^{-1} (vertical dotted line).

Figure 2 shows the relationship between the predicted EI_A by equation (3) and the experimentally derived EI_A values (based on measured peak drug concentrations in milk) of the 33 drugs. The regression was characterized by the following equation ($y = 0.87x + 2.08$; $r^2 = 0.502$; $P = 0.0001$). The 95% confidence intervals of the slope of the regression line were 0.55–1.18.

Discussion

The proposed exposure index introduces an important concept, namely that intra- or inter-individual differences in the M/P ratio of a drug due to variations in parameters such as milk pH and plasma protein binding can result in substantial changes in infant exposure if the clearance of the drug in the infant is sufficiently small. Conversely, if clearance is high, changes in the M/P ratio may have little clinically relevant influence on exposure of the infant to drug. Thus, a preference for using high-clearance drugs during breast-feeding is evident (Figure 1).

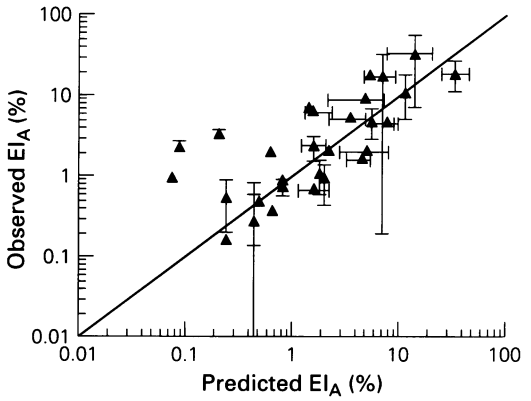

Figure 2 Relationship between predicted and observed EI_A values of 33 drugs. Predicted EI_A values (means ± s.d.) were calculated from theoretical M/P ratios and population average CL_A values. Observed EI_A values had been derived as the product of measured peak drug concentrations in milk and daily milk intake (150 ml kg^{-1}). Vertical bars indicate the ranges of the observed EI_A. The regression is given by: $y = 0.865x + 2.081$; $r^2 = 0.502$; $P = 0.0001$. The solid line represents the line of identity.

Drug clearance is generally decreased in neonates and premature newborns, especially in the early neonatal period. However, data are scarce for most drugs to indicate how low the clearance may be. Arbitrary correction factors (α = 10 for a post-conceptual age of 28–34 weeks; 3 for 34–40 weeks; 2 for 40–44 weeks; and 1.5 for 44–68 weeks) [4] may be applied as in equation (4). Importantly, the maternal administration of high-clearance drugs (e.g. 10 ml min^{-1} kg^{-1} and M/P ratio of 1) may not have a substantial influence on infant exposure (EI) even when the clearance in the infants is decreased to 20% of the adult value (a correction factor of 5). In contrast, the administration of low-clearance drugs may result in near therapeutic exposure in the infant. These findings argue further for preference for the use of high-clearance drugs during breast-feeding.

Figure 3a shows the distribution of average clearance values of 243 drugs in adults [6]; 82% have clearances of 1 ml min^{-1} kg^{-1} or greater. Figure 3b shows the distribution of the reported highest M/P ratios of 74 drugs [4]; 80% have ratios of less than 1. Therefore, our model implies that maternal administration of most drugs results in breast-fed infant exposures (EI_A) of less than 10% of those expected after therapeutic dosage directly to the infant. The experimental observations (Figures 1b and 3c) confirm this notion.

It is now possible to predict M/P ratios from the physicochemical characteristics of drugs [5, 9]. Hence, an initial estimate of EI can be calculated simply from equations (3) and (4) using the predicted

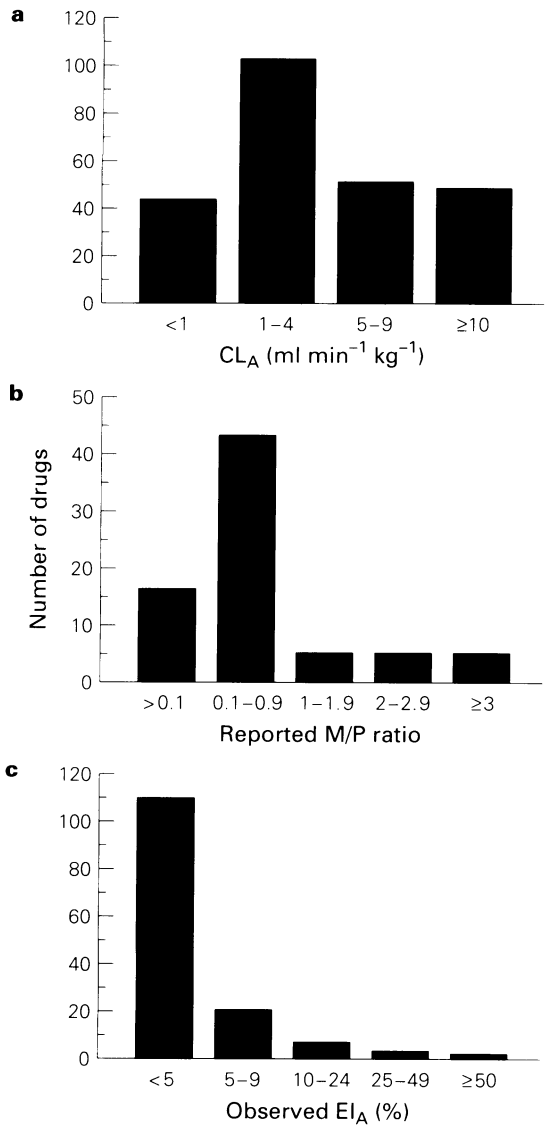

Figure 3 Distribution of experimentally derived values of drug clearance in adults (CL_A), milk-to-maternal plasma drug concentration ratios (M/P ratios), and infant exposure (EI_A). a) The population average values of CL_A of 243 drugs; 82% have CL_A values of 1 ml kg^{-1} min^{-1} or greater. b) The measured highest M/P ratios of 74 drugs; 80% have M/P ratios of less than 1. c) Observed infant exposure (EI_A) of 144 drugs derived from measured peak drug concentrations in milk; 90% have EI_A values of less than 10% of those expected after direct therapeutic doses.

M/P ratios, CL_A values reported in literature, and a correction factor. However, the regression of predicted on experimentally derived EI_A values shows large variability (Figure 2). This poor predictability may in part reflect the fact that clearance values in the population generally span 2- to 5-fold ranges. Moreover, whereas peak drug concentrations in milk were mostly used to calculate the experimentally derived EI_A values [4], we assumed average plasma drug concentrations at steady state (i.e. average drug concentrations in milk) in our calculation of predicted EI_A. Rigorous experimental estimates of average infant exposure are required to test the model.

The equations were derived to clarify the general principle of infant exposure to drug in milk; they are valid only when comparisons are made among different drugs under the aforementioned assumptions (Methods). When one assesses exposures of infants breast-fed by mothers with different C_{ss} of the same drug due to different clearance and/or doses, equations (1) and (3) may no longer be valid for comparisons because this violates the assumption that the dose, clearance, and C_{ss} are single average values for the drug. Individualization of the assessment necessitates another approach [2–4, 9].

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