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# PHARMACOKINETIC PITFALLS IN THE ESTIMATION OF THE BREAST MILK/PLASMA RATIO FOR DRUGS

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## INTRODUCTION

We hold these truths to be self-evident. The concentration of a drug in milk is time dependent. Concurrence does not necessarily exist between milk and plasma drug concentration profiles. Presumed concurrence undermines the study design and weakens the reliability of data. A pharmacokinetic model is a requisite foundation for studies of drugs in breast milk. A test of the model applicable to each drug allows the most accurate estimates of the milk-to-plasma (M/P) ratio. Pragmatic utilization of study data is often a function of a valid M/P ratio as it impacts on an assessment of dose and safety for the nursing infant.

The milk-to-plasma (M/P) ratio of drug concentration is often used to estimate the dose of maternal drug delivered via breast milk to the infant. An accurate ratio applicable to different dose strengths and chronicity of dosing is very useful when the concentration of drug in a mother's plasma, but not in her milk, is known. An inaccurate ratio, or one that cannot be used under the desired clinical circumstances, produces erroneous estimates of the amount of drug in milk.

Pitfalls exist in the estimation of the M/P ratio. The most common one is an implicit assumption that milk and plasma drug concentrations parallel each other throughout dosing, i.e. that a concurrence exists between the milk and plasma drug concentration profiles. This review emphasizes this and other potential problems by developing pharmacokinetic models, simulating illustrations, and citing studies reported for a few drugs.



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A focused review cannot appropriately consider all aspects of this important subject. Additional information is available from recent reviews of a selective or comprehensive nature on the following topics: pharmacokinetics (1–5), general aspects (6–22), and safety evaluations (23–24). We hope that the reader who reviews work in this field will question study design as it impacts on the accuracy of the reported M/P ratio and consequently on the estimation of drug dose in milk received by the nursing infant.



## BACKGROUND

### *The Use of the M/P Ratio*

The M/P ratio is used essentially to estimate the dose of a drug in milk as a function of the maternal plasma drug concentration. The M/P ratio adjusts for the factors that can change this concentration in either fluid. For example, an increase in dose or the use of multiple doses is expected to produce a higher concentration of drug in plasma, and hence in milk, than a lower or single dose. The ratio between milk and plasma concentrations expresses these changes without the need for a nomogram of maternal drug dose versus concentration of drug in milk. The usefulness of a nomogram is limited by the multiple influences on maternal drug disposition. The M/P ratio captures the net result of maternal drug dosing and disposition, i.e. the resultant plasma concentration, and the transfer of drug into milk. However, the M/P ratio is not necessarily constant under all conditions and at all times after dosing of a particular drug. The ratio may be affected by factors that alter either the delivery of blood to the breast or the bidirectional transfer of drug between plasma and milk. Some of these factors include pharmacokinetic characteristics of the drug itself (e.g. deep-compartment distribution behavior), physiochemical properties of the drug (pKa) and pH of the milk, the period of lactation, the maturity of the milk, the frequency of suckling, and maternal illness. These may perturb the expected concurrence of the milk and plasma drug concentration profiles and hence destabilize a M/P ratio determined under dissimilar conditions.

Utilizing the M/P ratio for the estimation of infant drug dose via breast milk is shown by the equations in Table 1 (3). An interdose plasma average is often used for the M/P ratio. Use of this equation presupposes a concurrence of milk and plasma profile during the dosing interval. It also presupposes that the M/P ratio for a single dose is the same as that for multiple dose administration under steady state conditions.

### *Prerequisites for an Estimate of Drug Concentration in Breast Milk*

As emphasized previously (4), three components are needed for a comprehensive study of drug dosing via breast milk: maternal pharmacokinetics, mam-

**Table 1** Drug dose given to infant via breast milk[a]

General calculation

$C_{avg} \times M/P \times$ milk volume (ml/kg/d) = dose (mg/kg/d)

Worse case analysis

$C_{max} \times M/P \times$ milk volume (ml/kg/d) = dose (mg/kg/d)

$C_{avg}$ and $C_{max}$ are respective averages and maximum drug concentrations in plasma at time of feeding. M/P is the milk to plasma ratio of drug concentration and is assumed to be invariate with regard to time after dosing.

Milk volume average is 150 ml/kg/d.

[a]Taken from (3).

**Table 2** Interrelation of factors in mother and infant as they affect drug dose in milk and safety to infant

- Milk concentration of drug a function of
  - maternal plasma concentration a function of
    - dose size and duration of dosing
    - clearance and time to $C_{ss}$
  - time of suckling in relation to
    - dosing
    - plasma drug $t_{1/2}$
  - M/P ratio a function of
    - transfer kinetics[a]
- Daily drug dose to infant a function of
  - → milk concentration (average per day)
  - milk volume consumed per day
- Infant plasma concentration a function of
  - → dose to infant per day
    - ADME[b] of infant
    - Safety in infant a function of
      - observed effects
      - → dose expressed as a function of
        - body weight
        - % of maternal dose
  - → plasma level relative to normal therapeutic range
  - age regarding drug effects on growth and development
  - concurrent illness
  - pharmacologic properties of a drug

[a]Transfer kinetics is broadly defined as all those events that determine the concentration of drug in milk at a certain time.

[b]ADME is absorption, distribution, metabolism, and excretion of a drug.

mary pharmacokinetics, and infant pharmacokinetics. The first two components interact to determine the time course profile of the M/P ratio. Resultant infant plasma concentrations (as well as the estimated dose in milk) are used to assess safety in addition to the intrinsic pharmacologic properties of a drug. This review addresses maternal and mammary pharmacokinetics as determinants of the M/P ratio and hence the amount of drug in breast milk.

The cascade of events starts with the excretion of drug in breast milk and ends with assessment of safety for the nursing infant (Table 2). Milk is seldom analyzed for drug concentration, so estimates are usually derived from maternal plasma levels and a reported value for the M/P ratio. An error in the estimation of drug concentration in milk can confound an evaluation of safety unless plasma drug concentrations are analyzed in the infant. Such analyses should be done at the time of predicted steady state conditions in the infant; otherwise drug concentrations will be underestimated. When only the calculated dose in milk is used as a guide, an accurate M/P ratio is crucial.

Use of a single-point-in-time M/P ratio or an average ratio calculated with single-dose area-under-the-curve (AUC) data is not sufficient for all drugs. Neither ratio attests to the importance of the time-dependent variation of drug concentration in milk. This time dependency presents pitfalls in determining an accurate M/P ratio as well as estimates of drug dose in milk at the time of infant suckling.

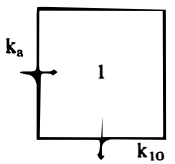


## PITFALLS IN THE ESTIMATION OF THE M/P RATIO

### *Applicable Models and Simulated Profiles of the M/P Ratio*

The M/P ratio is a function of the model that best describes maternal drug distribution and elimination. Drug profiles have been simulated for several models in order to show model-dependent effects on the M/P ratio as well as to illustrate the pharmacokinetic nature of pitfalls in estimation of the ratio.

A one-compartment open model, inclusive of central, peripheral, and milk compartments, is shown below:

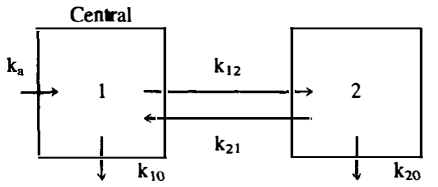



For this and subsequent models oral dosing is used and the absorption rate constant is $k_a$. The overall elimination rate constant is $k_{10}$. Simulations of each model utilize equations designed to elicit the amount of drug in a compartment. Conversion to drug concentration units requires information about the apparent

drug distribution volume of each compartment. This has not been assessed for each model nor is it important for the purpose of this review. The M/P ratios reported for the simulations illustrate the effects of particular combinations of pharmacokinetic rate constants on the amounts of drug rather than on drug concentrations. The resultant trend of M/P ratios for drug amounts should correspond closely to the trend of M/P ratios for drug concentrations in these models. However, the value of the M/P ratio for drug concentrations may not be the same as that for the M/P ratio for drug amount unless the apparent volumes of distribution for the two compartments are the same. For this and other models we have assumed that infant suckling does not occur or has no effect on the simulated profile[1].

A simulated drug concentration and derived M/P ratio profile for the one-compartment open model is shown in Figure 1. The M/P ratio essentially does not change in relation to time after single or multiple doses. The value of the M/P ratio for this and other simulations is determined solely by the pharmacokinetic parameters, without regard to drug-partitioning characteristics among fluids of different pH. It is quite likely that the distribution rate constants incorporate (or are largely a function of) the ion-partitioning characteristics of a drug. Observation of a similarity between the predicted and observed ultrafiltrate M/P ratio may require determining the M/P ratio under post-distribution conditions. This is apparent from a review of the following simulations, which emphasize the relative time dependency rather than absolute M/P ratio.

A two-compartment open model, including the peripheral and milk compartments, is shown as:




Corresponding simulations of drug amount in plasma and milk are shown in Figure 2. Note that the time dependency of the M/P ratio derived after a single dose is a function of the value of the distribution rate constants. A linear relationship has been found for the asymptotic value of the M/P ratio and the slope of the initial phase of the ratio obtained after a single dose. This relationship prevails in a two-compartment open model when the hybrid $\alpha$ rate constant is unchanged even though the $k_{12}/k_{21}$ ratio changes. However, the rate constants for $\beta$ and $k_a$ confound the relationship. Given these restrictions on the

[1]For example, $k_{20}$ in the succeeding two-compartment model has not been incorporated into our simulations.

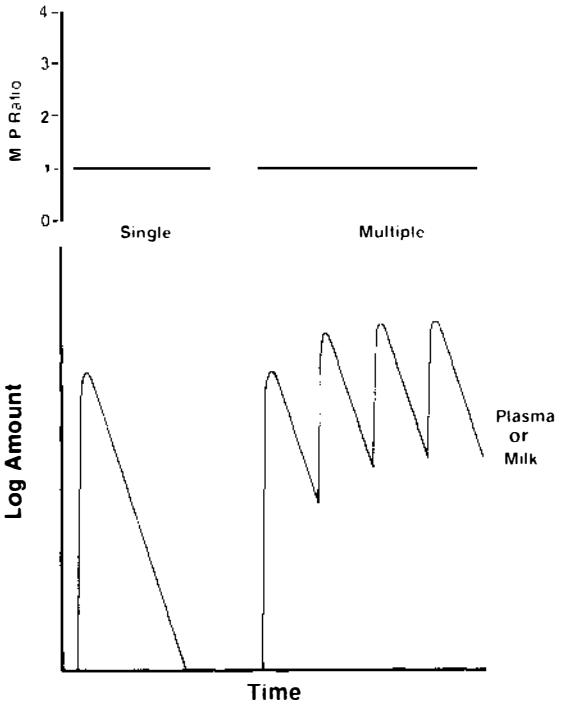



*Figure 1* Simulated profiles of milk and plasma drug amounts and derived M/P ratios for a one-compartment open model after single and multiple doses. Oral dosing and a one-compartment open model are assumed. Suckling did not occur. Pharmacokinetic parameters used for the simulation are: $k_a = 5.35$, $\beta = 0.4$ hour$^{-1}$. The dosing interval is three hours.

relationship, it is apparent that a higher M/P ratio, as observed with weakly basic drugs, is probably associated with a greater degree of change in the M/P ratio during early post-dose periods. A concentration-time profile must be described for such drugs in order to derive an accurate M/P ratio.

Figure 3 shows simulations of the drug amount and M/P ratio profiles for a two-compartment open model after multiple doses. It is apparent that the M/P ratio for single or multiple doses is a function of the time at which it is determined after dosing. This time dependency is exaggerated for drugs with rate constants similar to those used for Figure 2B and 2D, as shown by parts A and B of Figure 3. The deep-compartment behavior of a drug in milk, as shown by the simulation in Figure 4, produces a more marked change in the M/P ratio as dosing continues. In this example, the M/P ratio increases as a function of dose number. This is expected for filling a deep compartment. Accurate determination of the M/P ratio requires information about the drug-

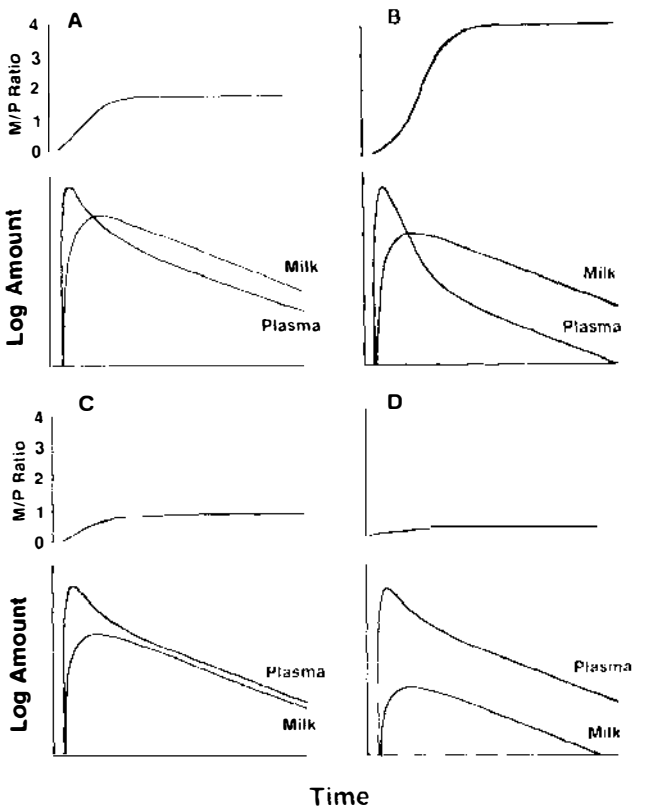



*Figure 2* Simulated profiles of milk and plasma drug amounts and derived M/P ratios for a two-compartment open model after a single dose. Oral dosing and a two-compartment open model are assumed. Suckling did not occur. Equations for this model as described in (25, 26) were used. Pharmacokinetic parameters for each part of this figure are:

| | A | B | C | D |
|---|---|---|---|---|
| | ($hour^{-1}$) | | | |
| $k_a$ | 4.0 | 4.0 | 4.0 | 4.0 |
| $k_{e1}$ | 0.2 | 0.2 | 0.2 | 0.2 |
| $\alpha$ | 1.5 | 1.5 | 0.56 | 0.272 |
| $k_{10}$ | 0.53 | 1.0 | 0.37 | 0.25 |
| $k_{12}$ | 0.60 | 0.4 | 0.087 | 0.0047 |
| $k_{21}$ | 0.56 | 0.3 | 0.30 | 0.22 |

concentration time-course profile in each fluid after a dose as well as the number of doses preceding the profile.

The three-compartment open model can exist in several forms, two of which are shown below:

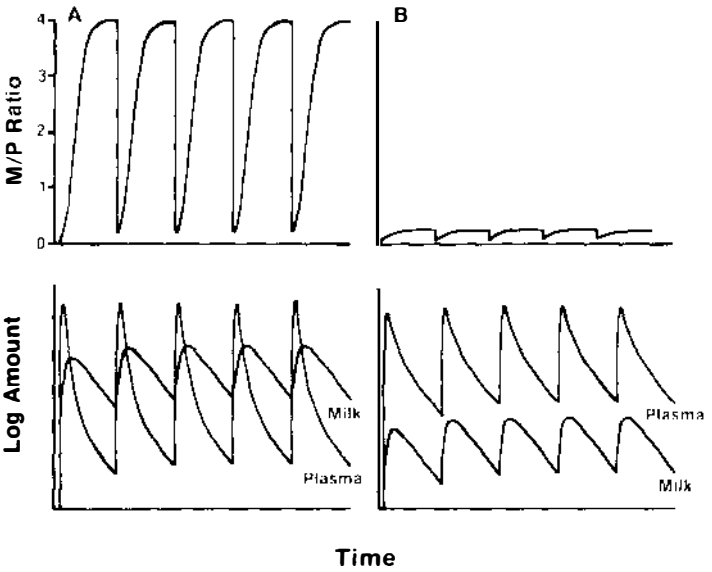



*Figure 3* Simulated profiles of milk and plasma drug amounts and derived M/P ratios for a two-compartment open model after multiple doses. Pharmacokinetic parameters shown for Figure 2B and 2D were used for parts A and B of this figure respectively. A dosing interval of eight hours was used and plasma steady-state conditions are shown.

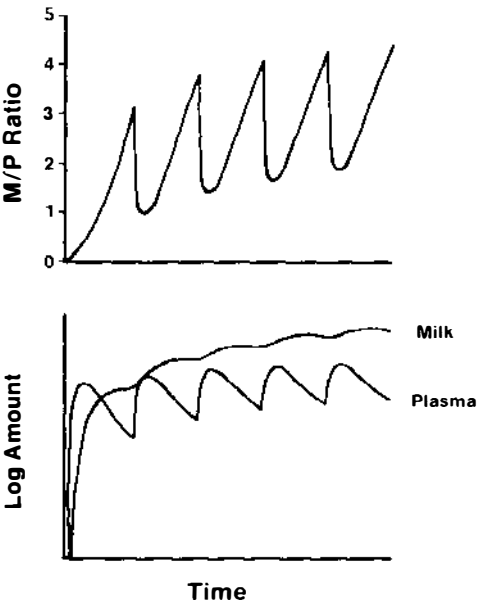
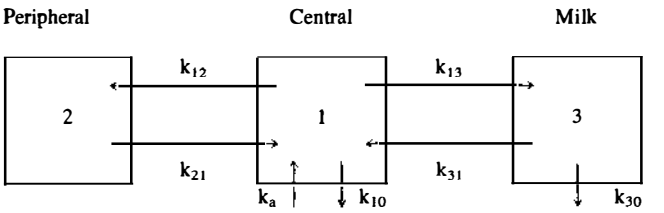


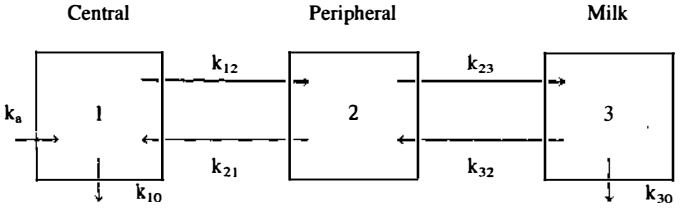

*Figure 4* Simulated profiles of milk and plasma drug amounts for a two-compartment open model: dose number and interval dependency of the M/P ratio. The parameters are: $k_a = 0.7$, $k_{el} = 0.0318$, $\alpha = 0.5$, $k_{10} = 0.1987$, $k_{12} = 0.2531$, $k_{21} = 0.08$ hour $^{-1}$. The dosing interval was every eight hours and dosing continued to attainment of plasma steady-state conditions.

Mamillary




Simulations for this model are likely to be similar to those for the two-compartment open model. Note that compartment #3 (milk) can be either deep or shallow and may not necessarily have the same characteristics as compartment #2. An example of milk as a deep compartment in this model is shown by the simulation in Figure 5. An enhanced M/P ratio occurs with each successive dose and depends on both dose number and interdose interval.

Sequential




In this model, milk compartment #3 contains a drug amount limited by that of compartment #2. This model was suggested previously, as was the mamillary model above (2). Either model allows the depth (and capacity) of the milk compartment to be estimated in a manner that distinguishes it from other compartments. This is advantageous since breast blood flow and milk production may alter the characteristics of the milk compartment irrespective of other compartments during various periods of lactation. It is not appropriate to assume that the characteristics of a peripheral compartment as determined by an analysis of plasma drug disposition are also applicable to the milk compartment. An analysis of drug concentration in both plasma and milk at various post-dose intervals may allow each compartment to be distinguished so that a model that best fits the data can be selected. Simulations of profiles for the sequential three-compartment open model are shown in Figure 6. The M/P ratio is a function of transfer kinetics operative for all three compartments and this

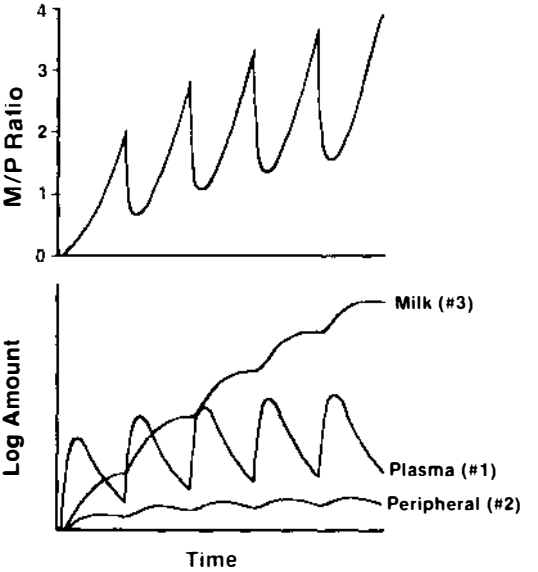



*Figure 5* Simulated profiles of milk and plasma drug amounts for a mamillary three-compartment open model: dose number and interval dependency of the M/P ratio. The compartment corresponding to each fluid is numbered. The following pharmacokinetic parameters were used for this simulation: $k_a = 0.7$, $\alpha = 0.52$, $\beta = 0.184$, $\gamma = 0.026$, $k_{10} = 0.2$, $k_{12} = 0.08$, $k_{21} = 0.25$, $k_{13} = 0.15$, $k_{31} = 0.05$ hour$^{-1}$. The dosing interval was every eight hours to the point of steady state. Milk is the third compartment and suckling did not occur (i.e. $k_{30} = 0$). The following differential equations were used to prepare the simulation:

1. $dXa/dt = -k_aX_a$
2. $dX_1/dt = k_aX_a - (k_{10} + k_{12} + k_{13})X_1 + k_{21}X_2 + k_{31}X_3$
3. $dX_2/dt = k_{12}X_1 - k_{21}X_2$
4. $dX_3/dt = k_{13}X_1 - (k_{30} + k_{31})X_3$

$X_i$ is the amount of drug in compartment i, and $k_{ij}$ represents the transfer rate constant between two compartments. Since suckling is assumed not to occur, $k_{30}$ can be set to zero. The solution was obtained by using input and disposition functions as described by Benet (27). Taking the Laplace transform of each equation yields a system of linear equations solvable by matrix algebra. Inverse transformation of the resulting solutions is accomplished using the general partial fraction theorem, as shown by Benet & Turi (28). For each compartment, the equation that relates the amount of drug in the compartment versus time contains the expected four exponential terms and this was used to construct the simulations. Programs using these solutions were executed by the Cromemco model Z-2D and Tektronix 4054 computers. Computation of $\alpha$, $\beta$, and $\gamma$ was accomplished by Bairstow's method for extracting polynomial roots.

produces a time dependency in the M/P ratio after a single dose. A dose-number dependency can also occur in this model (Figure 7). Caveats expressed about this finding in relation to the two-compartment and the mamillary three-compartment models are pertinent here also.

A four-compartment open model can contain features of the mamillary and sequential forms of the three-compartment open model:

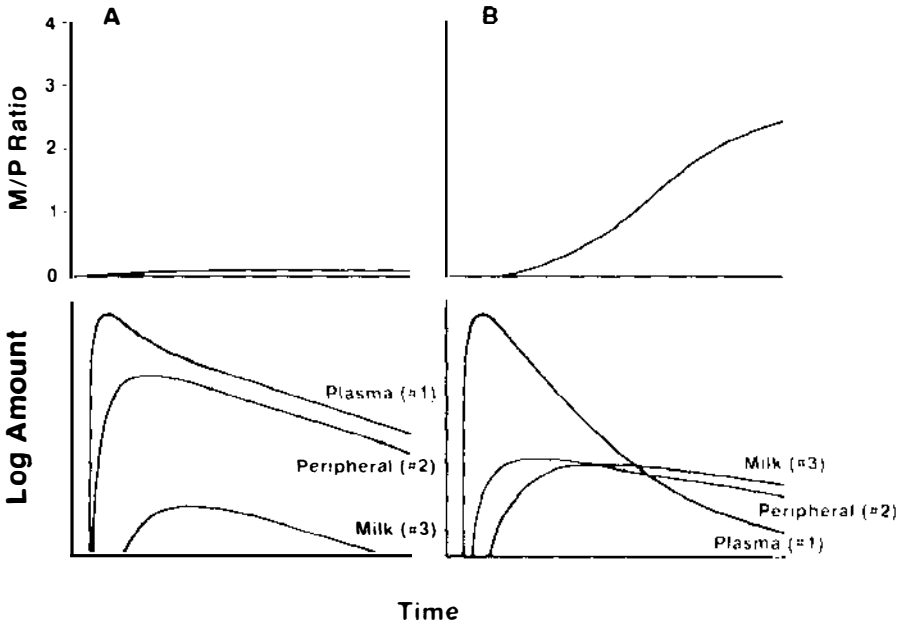



*Figure 6* Simulated profiles of milk and plasma drug amounts and derived M/P ratios for a sequential three-compartment open model after a single dose. See legend of Figure 5 for the development of mathematical solutions for this model needed to prepare the simulations. Pharmacokinetic parameters are:

| | A | B |
|---|---|---|
| | (hour$^{-1}$) | |
| $k_a$ | 3.87 | 3.87 |
| $\alpha$ | 1.75 | 1.72 |
| $\beta$ | 1.02 | 0.73 |
| $\gamma$ | 0.20 | 0.10 |
| $k_{10}$ | 0.36 | 0.63 |
| $k_{12}$ | 0.50 | 0.10 |
| $k_{21}$ | 0.93 | 0.27 |
| $k_{23}$ | 0.11 | 0.80 |
| $k_{32}$ | 1.06 | 0.75 |

The simulation described by a sequential three-compartment open model was developed by use of differential equations where milk was the third compartment:

1. $dX_a/dt = -k_aX_a$
2. $dX_1/dt = k_aX_a - (k_{10} + k_{12})X_1 + k_{21}X_2$
3. $dX_2/dt = k_{12}X_1 - (k_{21} + k_{23})X_2 + k_{32}X_3$
4. $dX_3/dt = k_{23}X_2 - (k_{30} + k_{32})X_3$

$X_i$ is the amount of drug in compartment i, and $k_{ij}$ represents the transfer rate constants between two compartments. Since suckling is assumed not to occur, $k_{30}$ can be set to zero.

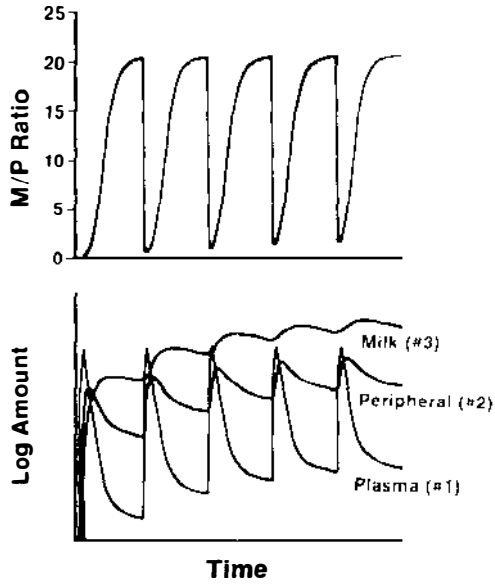
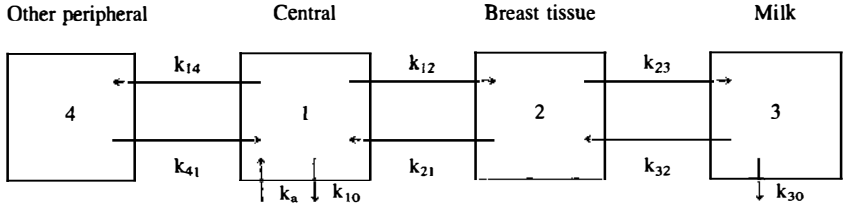



*Figure 7* Simulated profiles of milk and plasma drug amounts for a sequential three-compartment open model: dose number and interval dependency of the M/P ratio. A dosing interval of twelve hours and the following pharmacokinetic parameters were used: $k_a = 2.5$, $\alpha = 1.45$, $\beta = 0.7595$, $\gamma = 0.02297$, $k_{10} = 0.63$, $k_{12} = 0.6$, $k_{21} = 0.2$, $k_{23} = 0.6$, $k_{32} = 0.2$ hour$^{-1}$. See legend of Figure 5 for development of mathematical solutions for this model needed to prepare the simulations. Suckling did not occur (i.e. $k_{30} = 0$). A further exaggeration of the M/P ratio dose number dependency pattern is seen when $k_a = 1.5$, $\alpha = 1.174$, $\beta = 0.3726$, $\gamma = 0.0132$, $k_{10} = 0.9$, $k_{12} = 0.25$, $k_{21} = 0.08$, $k_{23} = 0.25$, and $k_{32} = 0.08$ hour$^{-1}$.




This model allows breast tissue (as a specific peripheral compartment #2) to be distinguished from other peripheral compartments, including milk (#3). Physiological changes in lactation are expected to make compartment #2 discernable. This model allows a study of drug-transfer mechanisms from the central

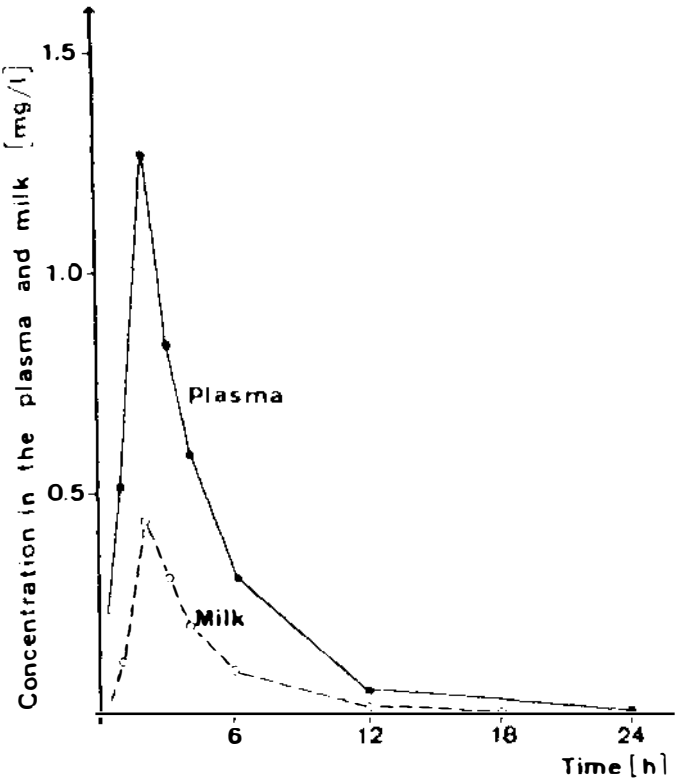



*Figure 8* Praziquantel concentrations (mg/l) in breast milk and plasma at various time intervals after a single oral dose of about 50 mg/kg. The arithmetic mean of data from five women studied by Putter et al (29) is shown.

to the milk compartment. Mathematical solutions for this model are being developed.

## *Reported Profiles of Milk and Plasma Drug Concentrations*

Reported examples of milk and plasma drug concentrations illustrate the time dependent nature of the M/P ratio as predicted from the simulations illustrated above. This ratio has been calculated for several reported drug studies in order to emphasize presence or absence of a concurrent profile for drug in plasma and milk. A concurrent profile is one in which the M/P ratio remains relatively flat following single or multiple drug doses. This has been found for several drugs after a single-dose administration to lactating women. The concentration profiles for a single dose of praziquantel (Figure 8) (29) are typical. The M/P ratio at any time after dosing is generally applicable to any other time, and a reliable average dose in milk can be estimated from an M/P ratio calculated from

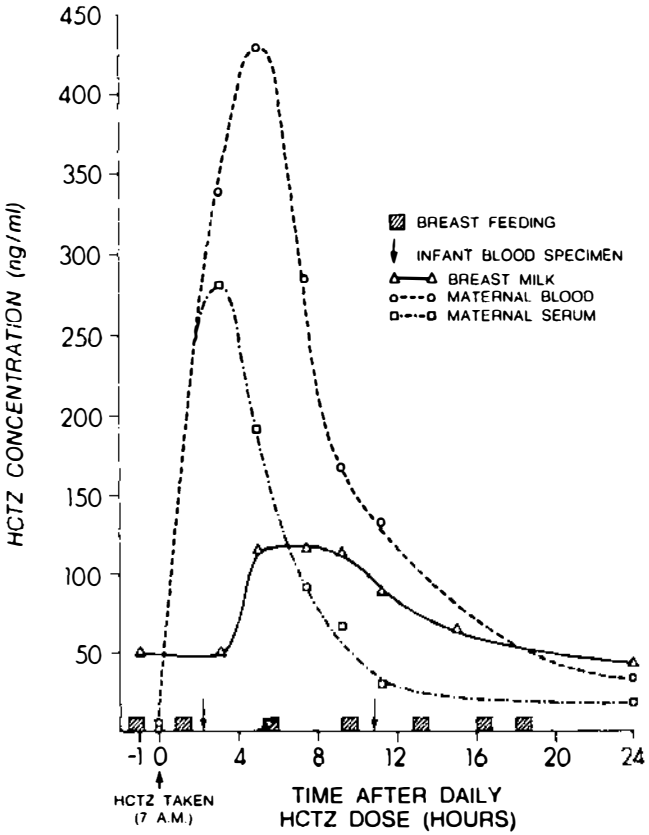



*Figure 9* Hydrochlorothiazide concentrations in breast milk, blood and serum over a 24-hour dosing interval. The two indicated blood specimens from the baby showed no detectable hydrochlorothiazide. Interdose data were obtained from a woman studied by Miller et al (30).

concentration or AUC data. Concurrent profiles found for single doses should be tested under steady-state conditions for lack of change in the observed M/P ratio.

A perturbed concurrence between milk and plasma drug concentrations is found for several drugs. The concentration of drug in milk and the timing of breast feeding to deliver the lowest amount of drug are affected accordingly. Previous reports show pitfalls in the M/P ratio caused by a lack of concurrent drug concentration profiles. A notable example is that of hydrochlorothiazide concentration in milk and plasma (Figure 9) (30). Nadolol milk and plasma concentrations show a marked difference with chronic dosing and after the drug is discontinued (Figure 10) (31). A similar single versus chronic dose discrepancy has been found for cimetidine such that the drug appears to accumulate in milk more than in plasma after multiple doses (32).

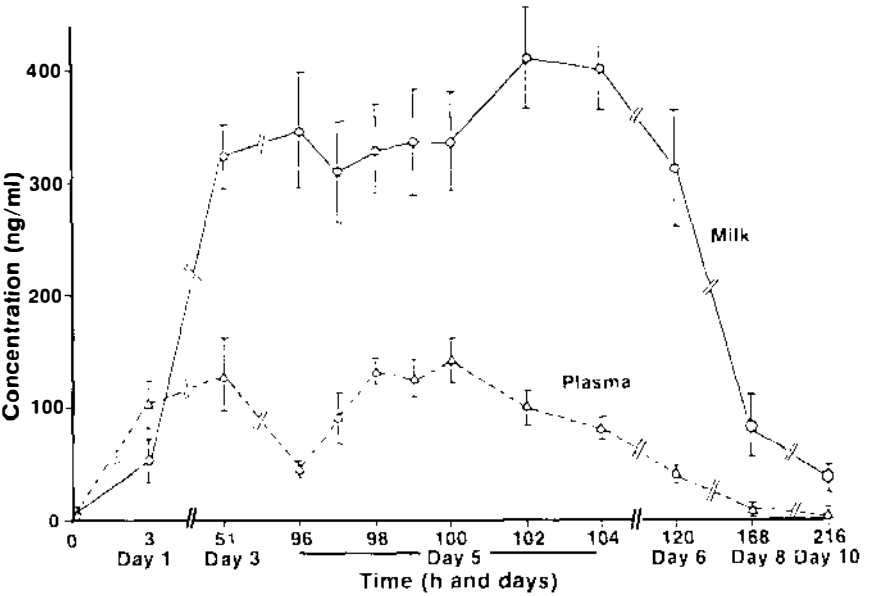



*Figure 10* Nadolol concentrations in breast milk and serum. The mean data from twelve subjects were obtained by Devlin et al (31). The drug was given once per day orally for five days.

The M/P ratios derived from reported milk and plasma drug concentration profiles are shown in Figures 11 and 12. The data are arbitrarily grouped for M/P ratios less than 0.2 and 0.2 to approximately one (Figure 11) and the same as or greater than one (Figure 12). Several observations of practical importance emerge from an analysis of M/P ratios for a wide variety of drugs. First, most drugs show a variable M/P ratio during the early periods following a dose. The variability appears to be less for drugs with an M/P ratio less than one. This is consistent with the relationship found between the initial slope and the asymptotic phase of the M/P ratio in profiles simulated for a two-compartment open model after a single dose. Second, a discrepancy in the single versus multiple dose M/P ratio has been found for nadolol and propranolol as seen in Figure 12 and as reported for cimetidine (32). This discrepancy is apparent with pharmacokinetic parameters used in our multiple dose simulations wherein a dose number dependency has been observed. Some drugs, notably those with an M/P ratio greater than one, may have milk distribution characteristics that enhance this discrepancy in single versus multiple dose M/P ratios. These are the drugs that may produce the highest concentrations in milk after multiple doses and hence may pose a risk to the infant. Overall, the derived M/P ratios in Figures 11 and 12 must be defined according to the post-dose interval and presumably also in relation to the single or multiple dose conditions. The third point of emphasis is that only eleven of the studies have data for more than one

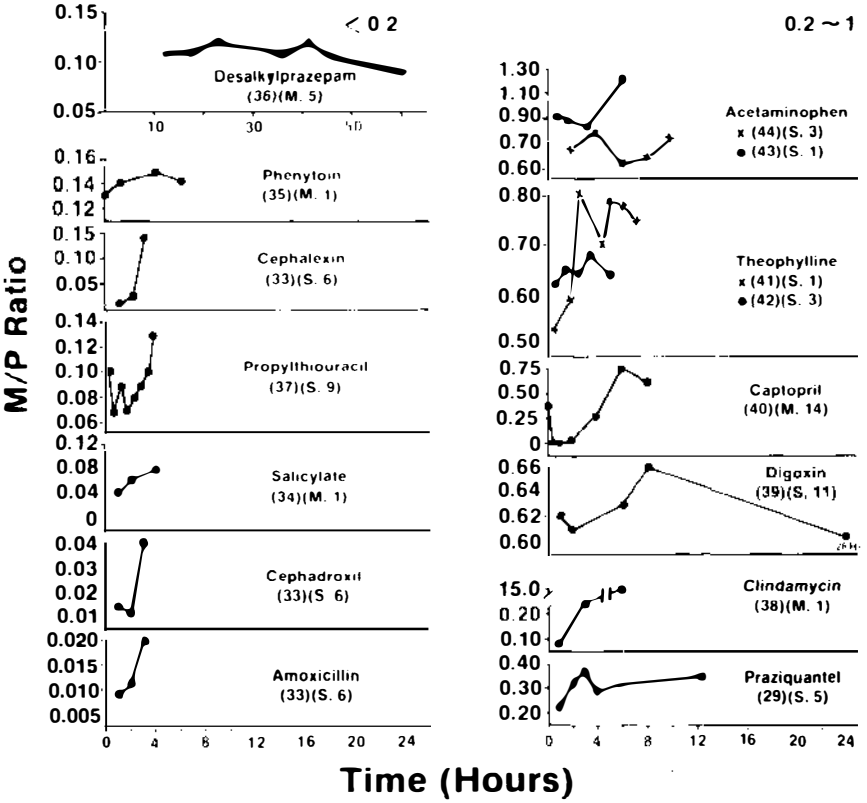



*Figure 11* Reported profiles of milk and plasma drug concentrations for a calculated M/P ratio of less than one. The milk and plasma (serum or blood) concentration data depicted in tables or graphs of the cited reference (first parenthetical number) was used to calculate the M/P ratio for each drug shown. Midpoint estimations and extrapolations by sight were used in some cases so that milk and plasma concentrations could be paired. The parenthetical material corresponds to data from a single (S) dose or after the administration of multiple (M) doses by the oral route. The number of patients is also shown. The metabolite of prazepam, desalkylprazepam, is shown because the parent drug was not detected in milk or plasma after three days of administration (36).

subject. It is difficult to apply a single subject–derived M/P ratio to the general population. Studies of appropriate design and in a sufficient number of lactating women are needed so that proposed models can be validated and generally applicable drug dose-in-milk calculations can be made.

## *Milk Volume and Its Constituent Effects on the M/P Ratio*

Our previous review (2) emphasized the effects of milk volume, pH, fat, and water on the total amount of drug excreted in breast milk. Less well appreciated (and apparently not well studied) is the role of these factors on the M/P ratio.

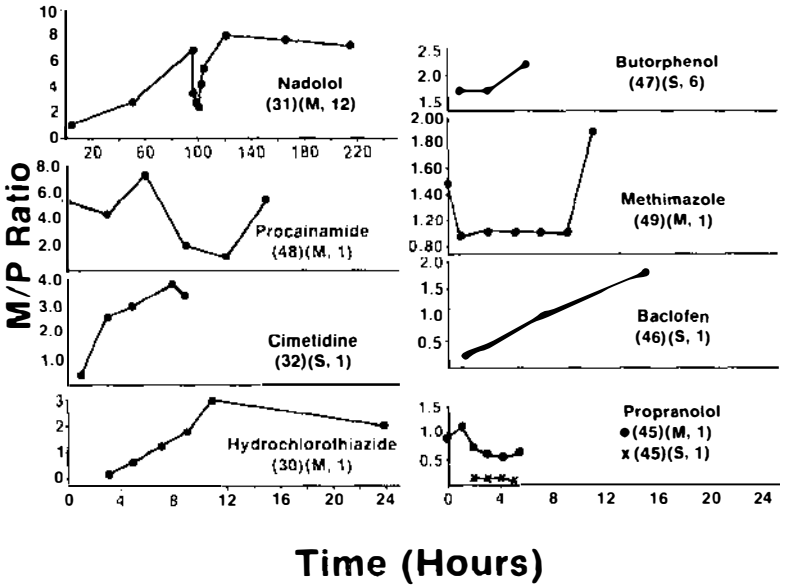



*Figure 12* Reported profiles of milk and drug concentrations for a calculated M/P ratio of greater than one. See legend of Figure 11.

For example, a weakly acidic and very fat-soluble drug may show a change in M/P ratio as a function of pH and fat content of milk, as predicted in Figure 13. These predicted effects are of practical importance, since milk pH and fat increase as a function of feeding time (fore versus hind milk) (50–51). A combined effect of milk fat and pH on the M/P ratio is probably reflected in the overall drug distribution rate constants as previously discussed. The possible contribution of these effects is seen in the relationship shown in Figure 13.

The quantity of drug in the milk compartment and the value of the M/P ratio are probably a function of both volume of milk and protein content as well as fat and pH. Each could give milk deep-compartment characteristics. In one study (44), the breast milk protein binding of acetaminophen was 13% that of plasma. This factor is quite likely reflected in the pharmacokinetic rate constants for a particular model.

## *Drug Metabolism Effects on the M/P Ratio*

While major attention is given to maternal drug disposition as it affects the M/P ratio, conceivable effects arise from in situ drug metabolism by breast tissue. This could limit the entry of drug to milk or selectively enhance drug metabolite excretion in milk. This is another phenomenon that could be incorporated by rate constants that fit a pharmacokinetic model. The inhibition of drug binding to milk protein via metabolite competition for binding sites is also possible. The

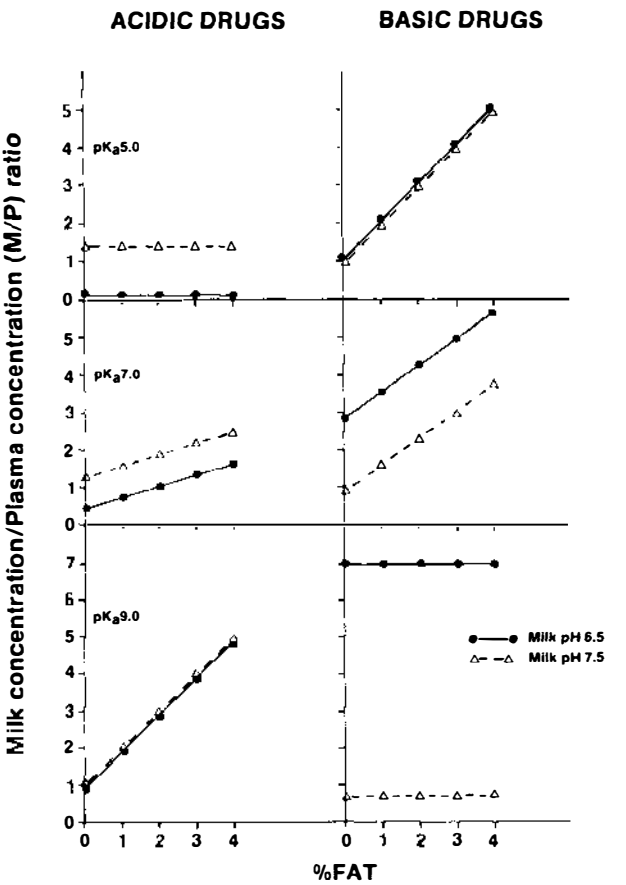



*Figure 13* Predicted change in the M/P ratio with increasing milk fat content. For these predictions, it was assumed that breast milk volume is much less than plasma volume, so that changes in M/P ratio do not cause plasma concentration to change. It was also assumed that the drugs were 100 times more soluble in fat than in water and that milk behaves as a simple two-phase system at the point of equilibrium with plasma. Acidic and basic drugs of various $pK_a$ are shown.

excretion of drug metabolites, either formed in situ or elsewhere, in breast milk should be examined with an approach not unlike that used for the parent drug. Metabolites in breast milk have been shown for the following drugs: disopyramide (52), procainamide (48), salicylazosulfapyridine (53, 54), isoniazid (55), and prazepam (36). Metabolites of antipyrine (56) and acetaminophen (43) have not been found in breast milk. An extensive analysis (57) has revealed multiple drug metabolites in breast milk after the administration of a combination drug product containing aspirin, caffeine, phenacetin, and codeine (Table 3). The M/P ratio of these drugs does not necessarily correspond

**Table 3** M/P ratios of parent drug and metabolites[a]

| Time (hours) | Phenacetin | Acetaminophen | Codeine | Morphine | Salicylate | Caffeine |
|---|---|---|---|---|---|---|
| | | | *(M/P concentration ratio)* | | | |
| 0.5 | 0.54 | 0.40 | 1.35 | 0.23 | 0.01 | 0.31 |
| 1.0 | 0.84 | 0.38 | 2.55 | 0.99 | 0.02 | 0.57 |
| 1.5 | | | | | | |
| 2.0 | 0.88 | 0.65 | 2.52 | 1.56 | 0.03 | 0.86 |
| 3.0 | 0.55 | | | | | |
| 4.0 | 0.55 | 0.77 | 1.92 | 2.0 | 0.04 | 0.86 |
| 7.0 | 1.02 | 1.25 | 2.14 | 3.48 | 0.09 | 0.92 |
| 12.0 | 0.37 | 1.63 | 1.67 | 5.07 | 0.31 | 0.85 |
| | | | $(AUC_M/AUC_P)$ | | | |
| | 0.67 | 0.81 | 2.16 | 2.46 | 0.05 | 0.82 |

[a] Adapted from Findlay et al (57) and from data they supplied to us for their subject #1. Single-dose administration of a compound analgesic preparation containing aspirin, phenacetin, caffeine, and codeine was studied in one subject. Concentration values were used to calculate M/P ratios at times shown. Area under the curve (AUC) estimates were used to derive the average AUC ratios.

to the value- or time-dependent profile of their respective metabolites. The dose of drug metabolites in breast milk is important if such metabolites are pharmacologically active and/or require excretion by immature systems in the nursing infant.

### *Maternal Disease Effects on the M/P Ratio*

Breast feeding women who take medicines presumably do so for the treatment of an illness. The effect of illness per se on either the M/P ratio or amount of drug excreted in milk has not been systematically studied. Diseases known to affect the amount of free drug in plasma may change the amount of drug in milk and possibly the M/P ratio.

### *Drug Interaction Effects on the M/P Ratio*

Not unlike disease effects, the influence of drug-drug interactions on the M/P ratio has not been well studied. Competing for milk binding sites or transfer mechanisms are loci for potential drug interactions, with resultant changes in the M/P ratio as well as total drug excreted in milk. This includes the coexistence of metabolites as well as parent drug in milk.

### *Interindividual Differences in the M/P Ratio*

Each drug or biological factor discussed above may interact to give a distinct value to the M/P ratio in an individual at a certain period of lactation. The collective contribution has not been assessed in a controlled manner. That interindividual variation in the M/P ratio probably exists is shown by the wide range of percent of maternal dose in milk values for antipyrine (0.56–2.38%) (56). Other drugs with reported interindividual variation in either breast milk drug concentrations or the M/P ratio are atenolol and propranolol (58), methyldopa (59), lormetazepam (60), phenytoin, (35), valproic acid (61, 62), and dyphylline (63). These few existing population studies highlight the weakness of an M/P ratio derived from a single case report.

## CONCLUSIONS

This review of pharmacokinetic pitfalls in the M/P ratio serves as a guideline for the design of studies that formulate an M/P ratio applicable to drugs used by lactating women. Errors implicit in an uncritical interpretation of existing data are highlighted by an appreciation of these pitfalls. The M/P ratio is a very important factor in the equation used to calculate dose of drug in milk delivered to the nursing infant. It is this factor that corrects for dose strength, duration of dosing, and maternal variations in drug disposition. A systematic study of probable influences on the M/P ratio should yield a valid parameter for the

assessment of infant dose and for the safety of breast feeding by mothers who require drug therapy during lactation.

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