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Prospective evaluation of a model for the prediction of milk:plasma drug concentrations from physicochemical characteristics

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1 Milk:plasma (M/P) drug concentration ratios predicted by a model utilizing pKa, plasma protein binding and octanol:water partition coefficients have been compared with actual M/P values for 10 basic drugs.
2 There was a close relationship between predicted and observed M/P ratios with a coefficient of determination r^2 of 0.97. However, there was a proportional error.
3 The data were transformed by taking logs of predicted and observed (M/P + 1) values. Regression analysis resulted in an r^2 of 0.95, an intercept on the Y-axis not significantly different from zero and a slope not significantly different from one.
4 The 95% confidence interval around a single prediction revealed an error between 150% for the lowest and 23% for the highest M/P ratios. The error is therefore lowest for the drugs likely to have the greatest transfer into milk.
5 There was no significant bias in the predictions.
6 The model was refined by multiple linear regression analysis utilising the observed M/P ratios for the 10 basic drugs in addition to those of the original drugs. The revised equation resulted in an improvement in the explained variance.
7 Protein binding was the most important single predictor.
8 The results confirm that M/P ratios for basic drugs can be predicted accurately from their physicochemical characteristics.

Keywords milk:plasma ratio M/P ratio drugs in milk model

Introduction

All drugs pass into milk to some extent. The milk:plasma (M/P) ratio based on the areas under the respective concentration-time curves (AUCs) is useful to calculate likely infant exposure to drugs ingested by the mother during breast feeding. Unfortunately there are many drugs for which the M/P ratio is not known.

Models have been developed using stepwise linear regression for both acidic and basic drugs which enable the M/P ratio to be predicted utilising the drug's pKa, the plasma protein binding (P.B.) value and the octanol:water partition coefficient (Atkinson & Begg, 1990). The models are:

$$\ln M/P = 0.025 + 2.3 \ln(Mu/Pu) + 0.9 \ln(f_{u,p}) + 0.5 \ln K$$

for basic drugs. (Equation 1)

and

$$\ln M/P = -0.405 + 9.4 \ln(Mu/Pu) - 0.7 \ln(f_{u,p}) - 1.5 \ln K$$

for acidic drugs. (Equation 2)

where

$K = (0.955/f_{u,m}) * (0.045 + \text{milk:lipid } P_{app})$

Mu/Pu = milk:plasma unbound drug concentration ratio
$f_{u,p}$ = fraction of drug unbound in plasma (i.e. 1-P.B.)
$f_{u,m}$ = fraction of drug unbound in milk
P_{app} = apparent partition coefficient at pH 7.2.

For most drugs the $f_{u,m}$ and milk:lipid P_{app} are not known but can be predicted from the $f_{u,p}$ and log P (the octanol:water partition coefficient) respectively (Atkinson & Begg, 1988a, b).

The aim of this prospective study was to compare M/P ratios predicted using the model with measured M/P ratios for basic drugs as they have appeared in the literature.

Methods

A continual analysis of the literature for well-documented M/P drug ratios (based on AUC values, or consistent single time point measurements) has been undertaken since our predictive model was established

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(Atkinson & Begg, 1990). The literature was also searched for the pKa, log P and plasma P.B. values of each drug. Adequate information became available for 10 basic drugs (Table 1) and Equation 1 was used to predict M/P values. Predicted M/P values were then compared with the observed M/P values using both regression analysis and assessment of bias and precision.

Regression analysis was performed on both untransformed and transformed data. The 95% confidence limits were defined around the regression line of transformed data for both the line of best fit and for an individual prediction.

Bias and precision were assessed according to Sheiner & Beal (1981). Bias, or mean prediction error, was assessed as follows:

$$\text{Bias} = 1/N \sum_{i=1}^{N} \text{prediction error}$$

Precision, or root mean squared error, was assessed as follows:

$$\text{Precision} = [1/N \sum_{i=1}^{N} (\text{prediction error})^2]^{\frac{1}{2}}$$

The equation for predicting ln(M/P) ratios for basic drugs (equation 1) was then refined utilising the 10 new basic drugs in addition to those used to define the original model. This was performed, as previously, using multiple linear regression (Atkinson & Begg, 1990).

Table 1 Physicochemical parameters

Drug	*pKa*	*log P*[1]	*P.B.*
Temazepam	1.31[f]	1.79[f]	97.6%[g]
Mefloquine	9.1[b]	−1.25[b]	98%[b]
Zolpidem	6.2[h]	2.43[h]	92%[h]
Tiapamil	7.0, 9.2[m]	0.57[m]	75%[m]
Chlormethiazole	3.2[a]	2.12[i]	64%[a]
Moclobemide	6.3[c]	1.77[c]	50%[c]
Chloroquine	8.4, 10.8[a]	1.04[j]	55%[a]
Procainamide	9.2[a]	0.80[d]	15%[a]
Sotalol	8.3, 9.8[a]	−1.59[e]	< 1%[a]
Quazepam	1.5[k]	4.3[l]	95%[e]

(1) log P values are all transformed to their respective P_{app} at pH 7.2
(a) Vozeh *et al.* (1990)
(b) Personal communication. Medical Director Roche Products (NZ) Ltd.
(c) Pons *et al.* (1990)
(d) Personal communication. Astra Division, Pharmaco (N.Z.) Ltd.
(e) Hackett *et al.* (1990)
(f) Greenblatt *et al.* (1983)
(g) Benet *et al.* (1985)
(h) Pons *et al.* (1989)
(i) Kowaluk *et al.* (1981)
(j) Lüllmann *et al.* (1979)
(k) Personal communication. Essex Laboratories (NZ) Ltd.
(l) Hilbert *et al.* (1984)
(m) Hartmann *et al.* (1988).

Results

The 10 basic drugs studied, along with their physicochemical characteristics, are shown in Table 1. These drugs were diverse, with pKa values spanning eight orders of magnitude, log P values spanning five orders of magnitude, and P.B. values from < 0.01 to 0.98.

Predicted and observed M/P values for the 10 basic drugs are shown in Table 2. A wide range of values was again observed. A plot of $M/P_{predicted}$ versus $M/P_{observed}$ is shown in Figure. 1. The linear regression equation of best fit was $y = 0.23 + 0.72x$, with a coefficient of determination (r^2) of 0.97. Residuals were evenly distributed positively and negatively and without trend. However, observation of the raw data (Table 2) suggests proportional rather than constant error necessitating transformation of the data for a more detailed analysis of the predictive performance.

Table 2 Observed and predicted milk:plasma ratios

Drug	M/P_{obs}	M/P_{pred}	*References*
Temazepam	0.14	0.05	Dusci *et al.* (1990)
Mefloquine	0.15	0.09	Edstein *et al.* (1988)
Zolpidem	0.16	0.35	Pons *et al.* (1989)
Tiapamil	0.44	0.81	Hartmann *et al.* (1988)
Chlormethiazole	0.73	0.84	Tunstall *et al.* (1979)
Moclobemide	0.69	0.89	Pons *et al.* (1990)
Chloroquine	1.40[a]	1.42	Ette *et al.* (1987) Atkinson *et al.* (1990)
Procainamide	3.2	2.5	Pittard *et al.* (1983)
Sotalol	3.74[b]	2.63	Hackett *et al.* (1990) Wagner *et al.* (1990)
Quazepam	4.13	3.43	Hilbert *et al.* (1984)

a Milk:plasma ratios were reported at 2.86 and 0.36 (Atkinson *et al.*, 1990a), and 0.99 (Ette *et al.*, 1987). Average = 1.40.
b Milk:plasma ratios were reported from 2.43–5.64 (Hackett *et al.*, 1990). Also reported as 3.16 (Wagner *et al.*, 1990). Average = 3.74.

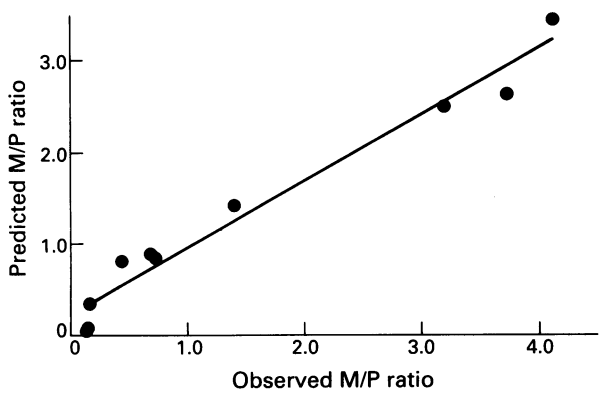

Figure 1 Plot of predicted *vs* observed M/P ratios. Equation of best fit $y = 0.23 + 0.72x$. $r^2 = 0.97$.

The data were therefore plotted as $\ln(M/P + 1)_{predicted}$ versus $\ln(M/P + 1)_{observed}$ (Figure 2). The linear regression equation of best fit was $y = 0.12 + 0.82x$, with an r^2 of 0.95 and even distribution of residuals. The intercept on the Y-axis was not significantly different from zero and the slope was not significantly different from one.

Bias and precision were also assessed on the transformed data. There was no significant bias, the mean value of −0.02 having 95% confidence limits of −0.13 to 0.09. Mean precision was calculated as 0.15, with 95% confidence limits of 0.13 to 0.17. If the upper limit of this confidence interval is used to assess the 'at worst case', precision is around 24% at the mean value for x of 0.72.

Perhaps a more meaningful assessment of the predictive performance of the model is afforded by an analysis of the 95% confidence limits of the line of regression, and of a single prediction (Figure 2). The 95% limits of a single prediction indicate the percentage error at all likely values of the M/P ratio. At the lower end of the regression line the percentage error is around 150%, at the mean 40%, and at the upper end 23%.

When the observed M/P values for the 10 basic drugs were included along with the original sample of 20 basic drugs to refine the model, the revised equation is:

$$\ln(M/P) = -0.09 + 2.54 \ln(Mu/Pu) + 0.79 \ln(f_{u,p}) + 0.46 \ln K$$

where the parameters are defined as for equation 1. The revised equation resulted in an r^2 of 0.87 in the multiple linear regression analysis compared with an r^2 of 0.83 with the original equation.

Assessment of the contribution of the individual components of the equation revealed that $\ln(f_{u,p})$ was the most important individual contributor to the M/P ratio. When $\ln(f_{u,p})$ was considered alone and a new equation was fitted in the form of $\ln(M/P) = a + b \ln(f_{u,p})$, where a and b are fitted coefficients, an r^2 of 0.48 resulted.

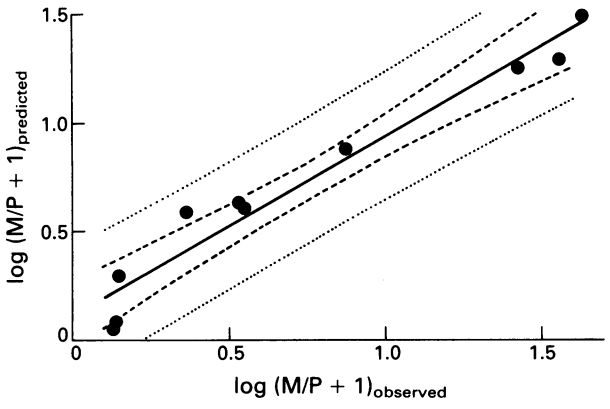

Figure 2 Plot of $\ln(M/P + 1)_{predicted}$ *vs* $\ln(M/P + 1)_{observed}$. Equation of best fit $y = 0.12 + 0.82x$. $r^2 = 0.95$. The 95% confidence limits of the line of best fit (--) and the 95% confidence limits of a single prediction (...) are included.

Discussion

The accuracy of predictions of M/P ratios must be considered in the context of the clinical situation when advice is needed about the safety of breast feeding during maternal ingestion of a drug. Where the M/P value is not known for a drug, breast feeding is usually considered contraindicated. By far the majority of drugs however are probably safe during breast feeding because the amount of drug received by the infant is very low (Atkinson *et al.*, 1990). Therefore, breast feeding is forbidden or the primary drug of choice avoided unnecessarily in many cases. Any model which enables prediction of the M/P ratio to even an approximate value would enable decisions about breast feeding to be made more rationally. It is the order of magnitude of the M/P ratio (i.e. 0.01, 0.1, 1, or > 1) rather than the precise value which is important. In this context, the model provides very accurate assessments of M/P ratios.

Figure 2 reveals that the percentage error is largest (150%) at extremely low M/P values (e.g. 0.1). Drugs with M/P ratios of this order are likely to be very safe during breast feeding (excluding those drugs contraindicated because of extreme toxicity), even if the maximum likely error of 150% is added to the estimate. It is the drugs with high M/P values which are likely to constitute problems in the suckling infant, and the model predicts these with considerable accuracy.

The model has been refined using the 10 new drugs from this study in addition to those used to define the original model. The refined model explains more of the variance in ln(M/P) ratios than the original model and is likely to be even more accurate in predictive performance.

Protein binding is the most important single parameter determining the diffusion of basic drugs into milk, itself explaining 48% of the variance in ln(M/P). This is easily confirmed by examination of Tables 1 and 2 where, with the exception of quazepam, an increase in M/P ratios is seen as P.B. declines. Quazepam has exceptionally high lipid solubility (log P of 4.3) which explains the high M/P ratio despite high P.B.

In summary, the model predicts M/P ratios without bias and with considerable accuracy for the clinical context. The model has been refined with improvement in the explained variance. A description of how to use the model to calculate M/P ratios and the likely infant concentrations that might result during breast feeding is included in Appendix 1 and 2.

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Appendix 1

Calculation of unknown M/P values for basic drugs

1) Obtain pKa, plasma P.B. and log P values from the literature.
2) Calculate Mu/Pu

$$\text{Mu/Pu} = \frac{1 + 10\,(\text{pKa} - 7.2)}{1 + 10\,(\text{pKa} - 7.4)}$$

where 7.2 and 7.4 represent the mean pH of milk and plasma respectively. Any pH value can be used.

3) Calculate fraction unbound in milk

$$f_{u,m} = \frac{f_{u,o}^{0.45}}{(6.94 \times 10^{-4})^{0.45} + f_{u,p}^{0.45}}$$

where $f_{u,p} = 1 - \text{P.B.}$

4) Calculate milk lipid P

$$\log \text{milk lipid P} = 1.29 \log \text{P} - 0.88$$

Antilog to get milk lipid P

5) Calculate K

$$\text{K} = (0.955/f_{u,m}) + (0.045 \text{ milk lipid P})$$

6) Calculate ln(M/P)

$$\ln(\text{M/P} = -0.09 + 2.54 \ln(\text{Mu/Pu}) + 0.8 \ln(f_{u,p}) + 0.46 \ln\text{K}$$

Antilog to get M/P.

Appendix 2

Calculation of likely infant plasma concentration

1) Calculate maternal steady-state plasma concentration (C_{mat})

$$C_{mat} = \frac{\text{Dose/h} * F_{mat}}{\text{CL}_{mat}}$$

where F_{mat} = maternal oral availability and CL_{mat} the maternal total drug clearance.

2) Calculate infant dose (mg kg^{-1} day^{-1}) in milk

$$\text{Dose/day} = C_{mat} \times \text{M/P} \times \text{V}_{milk}$$

where V_{milk} is the volume of milk ingested per day (usually 150 ml kg^{-1})

3) Calculate infant steady-state plasma concentration (C_{inf})

$$C_{inf} = \frac{\text{Dose/h} * F_{inf}}{CL_{inf}}$$

where F_{inf} = infant oral availability and CL_{inf} = the infant total drug clearance.

N.B. Where F_{inf} is not known, the assumption of equivalence with F_{mat} should not result in gross error.

Where CL_{inf} is not known, use the following table for approximate values.

Infant post-conceptual age	*CL*
28–34 weeks	$0.1 * CL_{mat}$
34–40 weeks	$0.33 * CL_{mat}$
40–44 weeks	$0.5 * CL_{mat}$
44–68 weeks	$0.66 * CL_{mat}$
> 68 weeks	CL_{mat}