ELSEVIER

Journal of Pharmaceutical and Biomedical Analysis
29 (2002) 103–119

JOURNAL OF
PHARMACEUTICAL
AND BIOMEDICAL
ANALYSIS

www.elsevier.com/locate/jpba

Molecular descriptors that influence the amount of drugs transfer into human breast milk

S. Agatonovic-Kustrin [a,*], L.H. Ling [b], S.Y. Tham [b], R.G. Alany [c]

[a] *School of Pharmaceutical, Molecular and Biomedical Science, University of South Australia, North Terrace, Adelaide 5000, Australia*
[b] *School of Pharmaceutical Sciences, Universiti Sains Malaysia, Penang 11800, Malaysia*
[c] *Division of Pharmacy, The University of Auckland, Auckland, New Zealand*

Received 11 January 2001; accepted 23 December 2001

Abstract

Most drugs are excreted into breast milk to some extent and are bioavailable to the infant. The ability to predict the approximate amount of drug that might be present in milk from the drug structure would be very useful in the clinical setting. The aim of this research was to simplify and upgrade the previously developed model for prediction of the milk to plasma (M/P) concentration ratio, given only the molecular structure of the drug. The set of 123 drug compounds, with experimentally derived M/P values taken from the literature, was used to develop, test and validate a predictive model. Each compound was encoded with 71 calculated molecular structure descriptors, including constitutional descriptors, topological descriptors, molecular connectivity, geometrical descriptors, quantum chemical descriptors, physicochemical descriptors and liquid properties. Genetic algorithm was used to select a subset of the descriptors that best describe the drug transfer into breast milk and artificial neural network (ANN) to correlate selected descriptors with the M/P ratio and develop a QSAR. The averaged literature M/P values were used as the ANN's output and calculated molecular descriptors as the inputs. A nine-descriptor nonlinear computational neural network model has been developed for the estimation of M/P ratio values for a data set of 123 drugs. The model included the percent of oxygen, parachor, density, highest occupied molecular orbital energy (HOMO), topological indices (χV2, χ2 and χ1) and shape indices (κ3, κ2), as the inputs had four hidden neurons and one output neuron. The QSPR that was developed indicates that molecular size (parachor, density) shape (topological shape indices, molecular connectivity indices) and electronic properties (HOMO) are the most important for drug transfer into breast milk. Unlike previously reported models, the QSPR model described here does not require experimentally derived parameters and could potentially provide a useful prediction of M/P ratio of new drugs only from a sketch of their structure and this approach might also be useful for drug information service. Regardless of the model or method used to estimate drug transfer into breast milk, these predictions should only be used to assist in the evaluation of risk, in conjunction with assessment of the infant's response.

Keywords: Milk to plasma ratio; Molecular descriptors; ANNs; GA; QSPR; QSAR

* Corresponding author. Tel.: +61-8-8302-2391; fax: +61-8-8302-2389.
E-mail address: nena.kustrin@unisa.edu.au (S. Agatonovic-Kustrin).

0731-7085/02/$ - see front matter
PII: S0731-7085(02)00037-7

1. Introduction

Breastfeeding is an essential physiologic process that provides nutrition and protects a child against infection and immunologic disorders. The frequency of various diseases and metabolic disorders are less in a breastfed infant. When drugs are administered to a nursing mother, a small part of them may appear in her milk [1]. Most drugs pass into breast milk, but the dose is reduced and usually does not produce a pharmacological effect. Certain drugs, however, do reach greater levels in milk than in the mother. Because of the infant's small size and the difference in metabolism between infants and adults, occasionally this transfer of medication can be harmful to the infant [2–4]. The amount of drug excreted into milk depends on a number of kinetic factors: (1) lipid solubility of the drug; (2) molecular size of the drug; (3) blood level attained in the maternal circulation; (4) protein binding in the maternal circulation; (5) oral bioavailability in the infant and the mother; and (6) half-life in the maternal and infant's plasma compartments.

Human milk is a suspension of protein and fat globules in a carbohydrate-based solution [5]. The mechanisms by which medications are transferred into breast milk are no different than those governing passage into any other maternal body fluid or organ system. Drugs enter milk primarily by passive diffusion reaching concentration equilibrium with the concentration in the blood, but also by active secretory methods that can concentrate the drug in the breast milk [6–8].

The most important determinant of drug penetration into milk is the mother's plasma level. Drugs enter milk and, in most cases, exit milk as a function of the mother's plasma level. Of the many factors, perhaps the two most important and useful are the degree of protein binding and lipid solubility. Drugs that are extremely lipid soluble penetrate milk in higher concentrations (i.e. CNS active drugs). Protein binding also plays a very important role. Drugs that have high maternal protein binding almost invariably produce lesser levels in milk. Most drugs circulate in the maternal plasma bound to a large molecular weight protein called albumin. An unbound component remains freely soluble in the plasma and transfers into milk, while the bound fraction stays in the maternal plasma unable to reach the tissues. For weak acids and bases, excretion into breast milk is governed by factors such as their pK_a, their concentration in plasma and the pH of the milk and plasma. In some instances, drugs become ion trapped in milk. Due to the lower pH of human milk, the physicochemical structure of the drug changes and prevents its perfusion back into the maternal circulation. Hence, they become ion trapped in the milk. Also, drugs may concentrate in the milk due to specialized transport systems, which 'pump' substances into the milk. In addition, a small water-soluble molecule, such as alcohol, may pas into the milk through aqueous pores in the membrane.

Assessing the risk of maternal medication to the breast-feed infant requires knowledge of the concentration of drug that might be present in the milk. This concentration can be calculated for a particular drug if the milk to plasma (M/P) concentration ratio is known for the drug. The M/P value is an attempt to identify the equilibrium concentration between breast milk and blood. It is equivalent to the drug concentration in the breast milk divided by the maternal serum concentration. As almost all drugs pass into milk from maternal plasma by passive diffusion, the M/P ratio is affected by the composition of the milk (aqueous, lipid, protein and pH) and the physicochemical characteristics of the drug (degree of ionization, molecular weight protein binding and lipophilicity).

Lower molecular weight drugs with high lipophilicity that are less protein-bound, nonionized, are more likely to diffuse into breast milk. The more lipid-soluble a medication, the more likely it will diffuse into milk. Breast milk has a lower pH (7.08) than plasma (7.42), causing weak bases to pass more readily into the milk than weak acids. Drugs that tend to concentrate in milk are weak bases, with low plasma protein binding and high lipid solubility. Additionally, medications may be transferred into breast milk incorporated within fat globules or bound to proteins, primarily casein and lactalbumin. Highly protein-bound drugs, though, are unlikely to cross

extensively into breast milk, since these drugs bind preferentially to serum albumin [9,10]. Finally, large molecules are not able to diffuse passively into the milk.

There is a tremendous need for more information on the safety of drugs while breastfeeding. The milk to plasma drug concentration ratios has been determined experimentally for many drugs. This ratio is most reliable when it comes from studies where the area under the concentration–time profiles has been measured over a whole dose interval. Unfortunately, most of the data on breastfeeding and drugs is based on single case reports or small case series. M/P data based on single time point concentration measurements in the two phases can be misleading because the time course of concentrations in milk and plasma may not parallel each other. Using these experimental data, empirical regression equations have been developed relating milk plasma ratio to the drug pK_a, the octanol water partition coefficient and plasma protein binding [11]. A log-transformed phase-distribution model appears to have good predictive performance [12]. The disadvantage of these methods is that plasma protein binding for the drug must be known or experimentally determined. Since these physico-chemical drug properties are not always available, a theoretical method that could predict the milk plasma ratio from the drug structure would be of interest.

The aim of this research was to simplify and upgrade a previously developed genetic neural network (GNN) model for prediction of M/P ratio given only the molecular structure of the drug [13]. The model is based only on theoretical molecular descriptors that can be calculated directly from molecular structure. This approach has potential use for drug information services when experimental physico-chemical properties of the drug are not available and experimental milk plasma ratios have not been investigated.

1.1. Artificial neural network (ANN)

An artificial neural network is a biologically inspired computer program designed to simulate the way in which the human brain processes information. ANNs are composed of hundreds of single processing elements (PE). Each PE has weighted inputs, transfer function and one output. PEs are connected with coefficients (weights) and are organized in a layered feed forward topology, the input layer, the output layer and the hidden layers between them. The number of layers and the number of units in each layer determines the function complexity.

Neural networks gather their knowledge by detecting the patterns and relationships in data and learn (or are trained) through experience with appropriate learning exemplars. The input layer neurons receive data from a data file. The output neurons provide the ANN's response to the input data. Units in the input layer do not process. They simply pass an output value onto units in the second layer. Each hidden or output unit performs a biased weighted sum of inputs and passes this activation signal through an activation function (also known as a transfer function) to produce their output.

Multilayer perceptron (MLP) is the most commonly used type of feed-forward network. MLPs use a linear activation signal or post synaptic potential (PSP) to combine incoming inputs and usually a non-linear activation function (also known as a transfer function). PEs are defined by their weights and threshold. Linear PSP units perform a weighted sum of their inputs, biased by the threshold value. Thus, a parameterized model is formed, with the weights and thresholds (biases) as the free parameters of the model. The standard activation function for MLPs is the logistic function. It is an S-shaped (sigmoid) curve, with output in the range (0.1).

When the network is executed, the input variable values are placed in the input units and then the hidden and output layer units are progressively executed. Each unit in the proceeding layers calculates its PSP of the neuron by taking the weighted sum of the outputs of the units in the preceding layer and subtracting the threshold. The activation signal is than passed through the activation function to produce the output of the neuron. When the entire network has been executed, the outputs of the output layer act as the output of the entire network.

2. Experimental

Neural Networks TM (StatSoft Inc., Tulsa) was used for building the QSAR model. For calculating drug properties from molecular structure, BioMed CAChe Project leader (Fujitsu America, Inc.) and ACD/ChemSketch (Toronto, Canada) were used.

2.1. Network training

The set of 123 structurally different compounds and their experimentally derived M/P values used in this study were collected from the literature. The M/P values were used as the ANN's output and 71 calculated molecular descriptors as the inputs. Before each training run, data sets were split randomly into three separate groups: training (83 data sets), testing (20 data sets) and validation (20 data sets) and both weights and biases were initialized with random values. The results of five runs were averaged. During training, the performance of the ANN was evaluated with testing data. The training set was used to train the network and the testing set was used to monitor overtraining the network. Training was stopped when the training root mean squared error (RMS) failed to improve over a given number of training cycles and when the testing RMS error started to increase. Validation set was used to evaluate the trained model.

The number of input and output neurons is defined by the problem. Input variables were selected based on their significance and physicochemical meaning. The number of hidden layers and neurons was optimized. A network with more input and hidden neurons has more weights, and models a more complex function and is likely to suffer from the over-fitting. A network with fewer weights may not be sufficiently powerful to model the underlying function. A network with no hidden layers models a simple linear function. Once the number of layers and the number of units in each layer was selected, the network's weights and thresholds were set in order to minimize the prediction error of the network. This is the role of the training algorithms.

2.2. Input variables selection

A neural network is usually treated as a black-box system, i.e. inputs are fed forward, weights are adjusted by back-propagation of the error and the outputs are saved. However, we wanted to look inside the box and to select significant inputs.

Inputs sensitivity analysis was used to specify significance of individual molecular descriptor and to select descriptors that are considered as most important. Variables with constant low sensitivity and high rating and uncertain variables with variable ratings that probably carry equally redundant information were regarded as insignificant and eliminated from the network.

Sensitivity analysis rates variables according to the deterioration in modeling performance that occurs if that variable is not included in the model. However, input variables are not independent and sensitivity analysis does not rate the significance of inputs in an absolute manner. It assigns a single rating value to each variable that cannot reflect the complexity and interdependence between variables. For that reason, a number of models with different topology were studied and variables that always had high sensitivity were identified as significant.

In addition, inputs activation was used to examine the activation level (outputs) of the input neurons. Inputs whose activation was equal to zero were eliminated.

2.3. Network design

Initial network configuration with one hidden layer and the number of hidden units set to half of the sum of the number of input and output units was generated. The number of hidden neurons and layer was optimized. Five experiments were conducted iteratively, with each configuration retaining the best network with the smallest validation error. Repeated training with each configuration was necessary to avoid undertraining of the network and stopping at the local minima. If the network did not achieve an acceptable performance level due to undertraining, more neurons or an additional hidden layer were added

to the hidden layer. In case of over-training (increase of the testing error), the number of hidden units or layers was reduced.

3. Results and discussion

The first step in developing QSAR was to calculate molecular descriptors. Seventy-one calculated structural features, including constitutional, topological, geometrical, quantum chemical and physicochemical descriptors, were generated for each drug molecule. The next step was to select descriptors that effect drug passage into breast milk.

Selection of the important molecular descriptors and examination of the variable contribution to the model through output sensitivity is an important aspect of QSRR study, not only for ranking the relative importance of each variable and calculating its statistical significance, but also as a means of refining the model by variable selection. Initially, MLP models with different topology were trained and tested. Best models, with low testing error and good predictive performance, were selected to perform sensitivity and to examine the activation level (outputs) of the input neurons. Inputs whose average activation was equal to zero and inputs with low sensitivity were eliminated. New MLP model with 32 inputs was established. Following this procedure, 14 inputs were selected in the same way for the next model, the number of inputs was reduced to 14 and finally to nine inputs (Table 1). The final model included percent of oxygen, parachor, density, highest occupied molecular orbital energy (HOMO), topological indices (χV2, χ2 and χ1) and shape indices (κ3, κ2), as the inputs had four hidden neurons and one output neuron. The QSPR that was developed indicates that molecular size (parachor, density) shape (topological shape indices, molecular connectivity indices) and electronic properties (HOMO) are the most important for the drug transfer into breast milk.

The octanol–water partition coefficient (log P) is frequently used in quantitative structure–activity relationships [14]. Partition coefficients thoroughly influence drug transport characteristics and the way drugs reach the site of action from the site of application (e.g. injection site, gastrointestinal tract, etc.). Since drugs are distributed via the blood, they must penetrate and traverse many cells to reach the site of action. Hence, the partition coefficient will determine what tissues a given compound can reach. Extremely water-soluble drugs may be unable to cross lipid barriers and gain access to organs rich in lipids, such as the brain and other neuronal tissues. Naturally, the partition coefficient is one of several physico-chemical parameters influencing drug transport and distribution, which itself is only one aspect of drug activity. Lipophilicity is basically a constitutive property. However, there is some degree of additivity and lipophilicity (log P) can be considered as an additive constitutive property. The contribution of each functional group and their structural arrangement influences the polarity and therefore the lipophilic or hydrophilic character of the molecule. Any given moiety with known lipophilicity can serve as a basic fragment from which the total lipophilicity can be construed by simple addition of the proper values. A correction term may be necessary to account for the constitutive changes introduced by the substituents, such as branching, double bonds, folding, intramolecular hydrogen-bonding, ring joining, etc. However, log P value contains limited information and becomes insufficient when topological or stereochemical features of molecules are analyzed in the context of inter-

Table 1
A subset of selected descriptors used as inputs in QSAR model, their sensitivity rating report and inputs activation values

Descriptor	Sensitivity rating	Input activation
Oxygen (%)	4.0	0.60
Parachor	7.5	0.17
Density	8.0	0.84
χV2	3.5	0.17
κ3	2.0	0.16
κ2	1.0	0.22
HOMO	4.5	0.75
χ2	6.5	0.26
χ1	8.0	0.29

molecular interactions with receptors. The model that was developed did not include lipophilicity, since the contribution of log P was smaller than that of other descriptors. Parameters that represent bulk properties, such as parachor and molecular connectivity indices that are directly correlated with log P were included.

The steric effects characterize bulk properties of a molecule and can be described with molecular mass, surface area, density and molar volume. The density of a substance is the ratio of its molecular mass to its volume and molar volume can be measured by determination of density of dilute solutions. Diffusion coefficients for hydrocarbon systems were successfully estimated from the molar density [15]. It is shown that the increase in density increases drug transfer to milk, perhaps due to a decrease in molar volume and hence molecular size. On the other hand, the lower the molecular mass of a medication, the more likely it is to penetrate into human milk, simply because diffusion through the alveolar epithelial cell is much easier. Medications with molecular weights < 300 are considered smaller and will tend to penetrate milk in higher concentrations than those with higher molecular weights. An example of a low molecular weight drug is ethanol (Alcohol). With a molecular weight of 120, it rapidly equilibrates between the plasma and milk compartments. Many of the amphetamines and diet medications unfortunately have low molecular weights as well. Drugs with molecular weights of 600 or greater are unlikely to penetrate milk in high concentrations. Typical examples of drugs with high molecular weights that are basically excluded from milk would include heparin (30,000) and insulin (6000).

Parachor [16] is an additive physical property of a substance also related to its molar volume and is determined by the kind and number of atoms in a molecule, as well as their manner of arrangement and binding. Increase in the parachor decreases M/P ratio. Small lipid insoluble substances penetrate cell membranes via the pores between aqueous phases on both sides of the membrane. The rate of such passive diffusion depends on the size of the pores, the molecular volume of the solute and the solute concentration gradient.

Over the last 10 years, a variety of topological and shape descriptors for the characterization of the molecular structure in combination with molecular dynamic analysis emerged as alternative descriptors in quantitative structure-activity studies [17,18]. The advantage of such descriptors is that they can be calculated for any chemical structure, real or hypothetical. Topological indices or numerical graph invariants constitute an important subset of these theoretical descriptors. They are suitable for describing similarity or dissimilarity of molecules. If two compounds have close values of a number of indices, they can be regarded as similar. Topological indices are derived from different classes of weighted graphs, representing various levels of chemical structural information. They are numerical quantifiers of molecular topology and encode information regarding the size, shape, branching pattern, cyclicity and symmetry of molecular graphs. A developed ANN model included topological shape descriptors of the second and third order, ($\kappa 2$ and $\kappa 3$), connectivity indices of the first and second order ($\chi 0 - \chi 2$) and valence connectivity index of the second order.

Topological shape indices [19] are the basis of a method of molecular structure quantification in which attributes of molecular shape and size are encoded into three indices (κ values 1–3). These indices are useful in quantification of shape similarity in contrast to the absolute quantification of size. The κ values permit a rational prediction of which molecule has a high degree of shape similarity. Electronic structure is encoded into other indices. A second application of the κ indices is its use to predict candidate molecule to fill molecular cavities. With the increasing use of molecular graphics, the fit docking or intercalation of molecules into cavities in macromolecular simulations, become an important consideration in drug design. First order shape attribute provides structural information related to complexity, or more precisely, on cyclicity of a molecule. The $\kappa 2$ index value encodes information related to the degree of star graph-likeness and linear graph-likeness. It encodes information about the spatial density of atoms in a molecule. The $\kappa 3$ values are larger when branching is non-existent or located at the

extremities of the graph. The κ3 value encodes information about the centrality of branching. The second order is defined by the count of two-bond paths and is related to the shape extremes represented by star graph or linear graph.

A developed model shows that an increase in κ2 decreases M/P ratio due to an increase in molecular size and lipid solubility, while the increase in κ3 (branching) promote drug transfer into breast milk. Molecular branching decreases molecular size, decreases molecular length and increases molecular complexity and perhaps decreases protein binding.

Molecular connectivity is a method of molecular structure quantification based only on bonding and branching patterns rather than physical or chemical characteristics. Weighted counts of substructure fragments are incorporated into numerical indices. Structural features, such as size, branching, unsaturation, heteroatom content and cyclicity are encoded. These indices are related to the number of atoms and how they are connected in a molecule. Only the carbon or heavy atoms are taken into consideration and the connectivity indices are derived from the hydrogen-suppressed graph of the molecule. Each atom is represented by a vertex in the graph, while the bonds becomes edges. Valence connectivity index [20] uses the same invariant but modifies vertex degrees to account for heteroatoms by using the number of valence electrons in the corresponding atom.

The molecular connectivity indices, χ values, describe the extent of skeletal branching. Connectivity indices are descriptor of molecular structure, a descriptor of size and shape based on a count of groupings of skeletal atoms, weighted by degree of skeletal branching. Each carbon atom in a molecular skeleton is assigned a number according to its number of neighboring carbon. The molecular skeleton is then fragmented into all its two carbon atom bonds. The sum of these values over the structure forms the χ index. Molecules could be further dissected into two bond fragments, three bond fragments and so on. Molecular structure is quantified so that weighted counts of substructure fragments are incorporated into numerical indices and an index is derived from a consideration of pairs of atoms forming bonds. The $\chi 0$, zeroth order (atomic) connectivity index, conveys information about the number of atoms in a molecule. The $\chi 1$ index encodes size and branching information. The $\chi 2$ encodes even more specific information about skeletal branching. These indices are correlated to molar volume [21]. Increase in $\chi 1$, (bond) and $\chi 2$ (path) connectivity indices decreases drugs transfer into milk. Molecular connectivity index of the first order, $\chi 1$, encodes single bond properties. It is a weighted count of bonds, related to the types and position of branching in the molecule. Molecular connectivity index of the second order, $\chi 2$, is derived from fragments of two-bond length. It also provides information about types and position of branching and may be an indication of the amount of structural flexibility. An increase in branching increases surface area and molecular volume [22] and results in the increase of solubility and lower partition coefficient. A statistical analysis has shown that $\chi 1$ and $\chi 2$ are covariant to an extent. However, there is enough difference between the information in $\chi 1$ and $\chi 2$ to reflect structural features contributing in a different way to the numerical value. The $\chi 2$ can differentiate between structural isomers, while $\chi 1$ values are identical. Low values of $\chi 1$ and $\chi 2$ are found for more elongated molecules or those with only one branching atom. An increase in the length of the carbon chain, non-polar portion of the molecule, results in the increase in lipid-solubility (log P) and an increase in molecular length.

Although solubility parameters, topological shape and connectivity indices are often successful in rationalizing solubilities and partition coefficients, they cannot account for conformational changes and they do not provide information about electronic influence through bonds or across space. For that reason, quantum chemical descriptors are used in developing QSAR. Quantum chemical descriptors can give great insight into structure and reactivity and can be used to establish and compare the conformational stability, chemical reactivity and inter-molecular interactions. They include thermodynamic properties (system energies) and electronic properties (LUMO or HOMO energy). Electronic properties may play a role in the magnitude in a biological

activity, along with structural features encoded in indexes. The developed model contained HOMO energy. Electronic effects are quantified explicitly by the use of molecular orbital calculations to estimate HOMO energy. In the case of an unsaturated compound, HOMO energy is a good descriptor that presents the distribution of π electron and explains π–π charge transfer interaction. The high electronic density and high frontier orbitals are present in molecules with high electron delocalization and can be used to predict biological reactivity. An increase in molecular reactivity also increases metabolic processes. Therefore, higher reactivity is to be expected for the molecules with higher HOMO energies. The HOMO energy plays a very important role in the nucleophylic behavior and it represents molecular reactivity as a nucleophyle. Good nucleophyles are those where the electron residue is high lying orbital. As expected, molecules with lower LUMO energy have a higher M/P ratio.

Chemical composition (weight percent of oxygen in molecular mass) also plays an important role. Presumably, weight percent of oxygen is related to the presence of the polar functional group. Polar functional groups account for many of the dipole–dipole, dipole-induced dipole and hydrogen bond interactions. They accommodate additional interaction in polar and in hydrogen-bonding compounds. Hydrogen bonding can be facilitated by the presence of hydroxyl groups. Dipole interactions are related to dipole moment of a whole molecule or part of a molecule, such as functional group, e.g. nitro. An increase in the weight percent of oxygen resulting in the increase in the high charge-transfer properties (dipole, nitro group) and hydrogen bonding, decreases drug transfer into milk and M/P ratio.

Predicted M/P values were within the range or close to the experimentally measured M/P ratio values (Table 2). In order to evaluate predictive performance of the final model, percent of testing and validation data set was gradually increased on account of the training data set and the relative error in prediction was monitored. Increasing the testing data up to 30% and validation data set up to 45% did not influence the network performance.

The predictive performance of the upgraded ANN model was better for basic drugs (cimetidine, mefloquine, morphine, methadone, nadolol) than that with the logarithmically transformed phase distribution model. For the logarithmically transformed phase distribution model, examinations of residual plot for acidic drugs indicated that penicillin was an outlier. The model also predicted lower M/P ratio for sertraline than the experimentally derived value taken from the literature. Study on the infants' serum sertraline concentrations show that the concentration of detectable sertraline is below the detection limit of most commercial laboratories [23]. The absence of detectable serum sertraline levels in the infant suggests that if medication were present in infant serum, its concentration would be extremely low [24]. Future studies of breast milk and infant serum samples should address these issues. Higher M/P values were predicted for ethanol, propranolol, oxprenolol, phenacetin, paracetamol, roxithromycin, minoxidil, zolpiderm, zonisamide, verapamil.

Alcohol can pass into a mother's milk very quickly and then out of the blood system (and milk) in a relatively short time, depending on the amount consumed. Alcohol levels in the milk peak 30–60 min after drinking or 60–90 min if the drink is taken with food. Beer has been used for years as a stimulant to breast milk production. This may be due to beer's ability to increase prolactin in men and non-lactating women. The active ingredient in beer is reported to be various B vitamins or 'Brewer's yeast'. Conversely, alcohol can inhibit milk ejection reflex in a dose dependent manner [25]. Several factors influence how much of a given drug, such as alcohol, will pass from the maternal circulation into the breast milk. Those factors include the pharmacokinetic properties of the drug and its metabolism, as well as the drug's solubility in water, pH, molecular weight and degree with which it binds to proteins [26]. Alcohol concentration in milk is similar to that in the blood and alcohol's elimination from blood and milk is closely correlated.

The fat and protein composition of human milk changes dramatically in the first several weeks postpartum. Milk whey and total proteins content

Table 2
Predictive performance of the developed model

Drug	Predicted M/P	Experimental M/P		
		Average	Minimum	Maximum
Acyclovir [29,30]	2.31	2.35	0.6	4.1
Amitriptyline [31–34]	1.28	1.53	0.5	1.93
Amoxycillin [35]	0.089	0.028	0.013	0.043
Amphetamine [36]	5.18	5.15	2.8	7.5
Ampicillin [37]	0.15	0.295	0.01	0.58
Aspirin [38–40]	1.05	1.63	0.06	3.2
Astemizole [41]	4.08	4.4	4.4	4.4
Atenolol [42,43]	2.16	2.1	1.1	3.1
Bupivacaine [44]	0.36	0.34	0.10	0.58
Bupropion [45]	5.43	5.545	5.545	5.545
Caffeine [46,47]	0.77	0.711	0.61	0.812
Cannabis [48]	3.88	4.24	0.08	8.4
Carbamazepine 10,11-epoxide [49,50]	0.85	0.79	0.79	0.79
Carbamazepine [50,51]	0.74	0.465	0.24	0.69
Carbenicillin [51]	0.058	0.02	0.02	0.02
Cefotaxime [52,53]	0.08	0.16	0.16	0.16
Cefoxitin [54]	0.04	0	0	0
Ceftriaxone [55]	0.08	0.045	0.03	0.06
Cephalexin [56]	−0.03	0.012	0.01	0.014
Chloramphenicol [57]	0.65	0.655	0.655	0.655
Chlorprothixene [58]	2.08	1.48	0.38	2.58
Cimetidine [59–61]	1.74	1.7	1.7	1.7
Ciprofloxacin [62]	1.5	1.495	0.85	2.14
Citalopram [63]	1.06	2.1	1.2	3.0
Clemastine [64]	0.54	0.375	0.25	0.5
Clofazim	1.46	1.35	1.35	1.35
Clomipramine [65]	0.92	1.03	0.84	1.22
Clonazepam [66,67]	0.23	0.33	0.33	0.37
Clozapine [68]	3.84	3.555	2.79	4.32
Codeine [69]	2.28	2.16	2.16	2.16
Cotinine [70]	0.74	0.78	0.78	0.78
Decarboetoxyloratadine [71]	0.89	0.8	0.8	0.8
Demethylcitalopram [64]	1.92	1.75	1.0	2.5
Desipramine [72,73]	0.92	0.915	0.63	1.2
Desmethyldoxepin [74]	1.32	1.275	1.02	1.53
Diazepam [75,76]	0.86	0.7	0.1	1.3
Diltiazem [77]	0.93	0.98	0.98	0.98
Disopyramide [78,79]	1.04	0.9	0.9	0.9
Dothiepin [80]	1.63	1.59	1.27	1.91
Dothiepsulfoxide [80]	1.12	1.18	0.89	1.47
Doxepin [75]	1.24	1.37	0.4	1.65
Doxycycline [42]	0.49	0.34	0.32	0.36
Erythromycin [42]	0.39	0.455	0.41	0.5
Ethanol [81,82]	2.72	0.9	0.9	0.9
Ethosuximide [83,84]	0.83	0.8	0.8	0.8
Flunitrazepam [85]	0.54	0.54	0.54	0.54
Fluoxetine [86]	1.07	0.68	0.52	0.84
Gentamicin [87]	0.47	0.44	0.44	0.44
Holoperidol [88,89]	0.50	0.64	0.59	0.69
Ibuprofen [90,91]	0.14	0	0	0
Imipramine [42,74]	1.25	0.76	0.76	0.76

Table 2 *(continued)*

Drug	Predicted M/P	Experimental M/P		
		Average	Minimum	Maximum
Indomethacin [92]	−0.11	0.19	0.01	0.37
Labetalol [93]	2.0	1.7	0.8	2.6
Lamotrigine [94]	0.25	0.425	0.4	0.45
Lidocaine [45]	1.27	1.07	0.25	1.89
Loratadine [72]	1.07	1.2	1.2	1.2
Lorazepam [95]	0.23	0.205	0.15	0.26
Medroxyprogesterone [96]	1.99	0.72	0.72	0.72
Mefloquine [97]	0.18	0.145	0.13	0.16
Mepindolol [98]	3.4	2.6	1.0	4.2
Methadone [99,100]	0.95	0.44	0.24	0.64
Methotrexate [101]	0.08	0.04	0.04	0.04
Methyldopa [102]	0.34	0.265	0.265	0.265
Metoprol [103]	2.48	2.55	2.0	3.1
Metronidazole [104–106]	1.11	0.95	0.9	1
Mexiletine [107]	1.55	1.34	0.79	1.89
Mianserin [42]	1.99	2.2	2.2	2.2
Minoxidil [108]	2.49	0.76	0.76	0.76
Moclobemide [109]	0.97	0.72	0.69	0.75
Morphine [110,111]	2.59	2.46	2.46	2.46
Nadolol [112]	4.65	4.6	4.6	4.6
N-desmethylsertraline [113]	1.01	1.64	1.64	1.64
Nefopam [114]	1.61	1.2	1.2	1.2
Nicotine [71,115]	1.7	2.25	1.5	3.0
Nitrazepam [42]	0.15	0.27	0.27	0.27
Nitredipin [116]	0.62	0.35	0.35	0.35
Nitrofuranthoin [117]	1.32	2.25	2.25	2.25
Nordothiepin [81]	1.39	0.85	0.69	1.01
Nordothiepsulfoxide [81]	1.69	1.86	1.57	2.15
Norethindron [42]	1.19	0.19	0.19	0.19
Norfluexetine [87]	0.63	0.56	0.56	0.56
Norfluoxetine [87]	0.81	0.56	0.35	0.77
Nortriptyline [118,119]	0.98	1.18	0.50	1.62
Noscapine [120]	0.96	0.29	0.29	0.29
O-desmethylvenlafaxine [121]	5.27	3.3	2.8	3.8
Oxazepam [122,123]	1	0.1	0.1	0.33
Oxprenolol [124]	1.42	0.37	0.37	0.37
Paracetamol [125,126]	5.28	0.88	0.76	1.0
Paroxetine [127–129]	1.09	0.75	0.39	1.11
Penicillin V [130]	0.39	0.37	0.37	0.37
Penicillin G	0.17	0.315	0.06	0.57
Perfenazine [131]	0.9	0.9	0.7	1.1
Phenacetine [132]	2.85	0.67	0.67	0.67
Phenobarbitone [133]	−0.14	0.5	0.4	0.6
Phenytoin [134,135]	0.03	0.363	0.142	0.584
Prednisolone [136,137]	0.14	0.13	0.13	0.13
Procainamide [138]	1.53	3.2	3.2	3.2
Propranolol [139,140]	2.99	0.403	0.107	0.699
Quazepam [141]	1.21	4.13	4.13	4.13
Quinapril [142]	0.42	0.12	0.12	0.12
Rosaramicin [143]	1.42	0.12	0.12	0.12

Table 2 *(continued)*

Drug	Predicted M/P	Experimental M/P		
		Average	Minimum	Maximum
Roxithromycin [144]	1.85	0.035	0.03	0.04
Satalol [145,146]	6.58	5.4	5.4	5.4
Sertraline [147,148]	0.28	1.275	0.62	1.93
Sulfamethoxazole	2.59	0.1	0.1	0.1
Sumatriptan [149]	4.11	4.9	4.1	5.7
Suprofen [150]	0.0001	0.014	0.014	0.014
Temazepam [151]	0.95	0.14	0.14	0.14
Tetracycline [42]	0.03	0.95	0.6	1.3
Theobromine [152]	0.89	0.82	0.82	0.82
Theophylline [153]	0.0001	0.7	0.7	0.7
Tiapamil [154]	0.41	0.44	0.43	0.45
Timolol [125]	1.4	0.8	0.8	0.8
Tinidazole [155]	3.36	1.005	1.005	1.005
Tolmetin [156]	0.15	0.005	0.005	0.005
Triprolidine [157]	1.21	0.53	0.5	0.56
Valproic acid [158]	0.72	0.053	0.01	0.096
Venlafaxine [122]	3.84	3.8	2.8	4.8
Verapamil [159]	2.55	0.6	0.6	0.6
Vigabatrin [160]	0.60	1	1.0	1.0
Zolpidem [161]	1.21	0.13	0.13	0.13
Zonisamide [162]	3.47	0.93	0.84	1.02
Zopiclone [163]	0.17	0.555	0.41	0.70

decreases as lactation progresses, but changes in fat levels are usually not statistically significant. Beta-adrenergic antagonists are one of the most commonly used class of agents in the treatment of hypertension, angina pectoris and certain arrhythmias. Experiments show that M/P ratio of propranolol increases during the first several weeks postpartum, due to changes in milk pH and total serum protein content [27]. The issue of prescription of analgesics during lactation is also complex. Most of the information available is based on single dose or short term studies and for many drugs only a single or a few case reports have been published.

Minoxidil has not been studied in pregnant women. However, there have been reports of babies born with extra thick or dark hair on their bodies after the mothers took minoxidil during pregnancy. Minoxidil passes into breast milk, it has not been reported to cause problems in nursing babies.

Norethindrone is a progestational agent. Although progestins pass into the breast milk, they have not been shown to cause problems in nursing babies. However, progestins may change the quality or amount (increase or decrease) of the mother's breast milk.

Roxithromycin, a new macrolide antibiotic is rapidly absorbed after oral administration. Peak plasma levels following 150 and 300 mg doses occur within 2 h. Steady state is reached within 4 days with doses of 150 mg twice a day or 300 mg once daily. The plasma half-life is ≈ 12 h.

Verapamil is known as a calcium channel blocker. Calcium channel blocking agents have not been studied in pregnant women. However, studies in animals have shown that large doses of calcium channel blocking agents cause birth defects, prolonged pregnancy, poor bone development in the offspring and stillbirth. Verapamil is excreted in breast milk. It may be necessary to change therapy or provide an alternate to breast milk.

All of the psychotropic medications studied to date pass into breast milk. The data regarding the degree of passage to the infant and the subsequent effects of this exposure on infant growth and development are very limited. The apparent elimination half life for zolpidem is 2.6 h. Experimen-

tal value for M/P ratio of the zolpidem 3 h after administration is 0.13 and no detectable zolpidem can be found in the milk at subsequent sampling times. Zolpidem belongs to the central nervous system (CNS) depressants. It is used to treat insomnia. Zonisamide, anticonvulsant is used in the treatment of epilepsy. It passes into breast milk. However, it is not known whether this medicine causes problems in nursing babies. Psychotropic medications pass into breast milk to some degree, mostly through the process of passive diffusion [15,16]. However, a drug's protein binding, lipid solubility, degree of ionization (or pK_a), and molecular weight also influence the extent of passage of a compound and the amount that remains in breast milk.

In addition, predicted M/P ratio for ibuprofen was slightly higher than the experimentally determined ratio. The absorption of ibuprofen is rapid and complete when given orally. The area under the plasma concentration–time curve (AUC) of ibuprofen is dose-dependent. Ibuprofen binds extensively, in a concentration-dependent manner, to plasma albumin. At doses >600 mg, there is an increase in the unbound fraction of the drug, leading to an increased clearance of ibuprofen and a reduced AUC of the total drug.

4. Conclusion

A nine-descriptor nonlinear computational neural network model has been developed for the estimation of M/P ratio values for a data set of 123 drugs. Unlike previously reported models, the QSPR model described here does not require experimental parameters and could potentially provide useful prediction of M/P ratio of new drugs and reduce the need for actual compound synthesis and M/P ratio measurements. Model can be used to estimate the activities of other molecules only from a sketch of their structure and this approach might also be useful for drug information service.

Regardless of the model or method used to estimate drug transfer into breast milk, these predictions should only be used to assist in the evaluation of risk, in conjunction with assessment of the infant's response.

Toxicity in the infant is not the only potential adverse effect of maternal medication use. Recent research has revealed an effect on infant metabolism. Maternal use of medications, which induce hepatic metabolism, appears to stimulate the breastfeeding infant's liver as well as the mother's. In a similar manner, drugs that inhibit metabolism have been found to slow function in both mother and child [28].

References

[1] S. Kacew, Adverse effects of drugs and chemicals in breast milk on the nursing infant, J. Clin. Pharmacol. 33 (1993) 213–221.
[2] C.R. Howard, R.A. Lawrence, Drugs and breastfeeding, Clin. Perinatol. 26 (1999) 447–478.
[3] K. Yoshida, B. Smith, M. Craggs, R. Kumar, Neuroleptic drugs in breast-milk: a study of pharmacokinetics and of possible adverse effects in breast-fed infants, Psychol. Med. 28 (1998) 81–91.
[4] A. Lewellyn, Z.N. Stowe, Psychotropic medications in lactation, J. Clin. Psychiatry 59 (Suppl. 2) (1998) 41–52.
[5] G.G. Briggs, R.K. Freeman, S.J. Yaff, Drugs in Pregnancy and Lactation, fourth ed, Williams and Wilkins, Baltimore, 1994.
[6] C.Y. Oo, R.J. Kuhn, N. Desai, P.J. McNamara, Active transport of cimetidine into human milk, Clin. Pharmacol. Ther. 58 (1995) 548–555.
[7] F.W. Kari, R. Weaver, M.C. Neville, Active transport of nitrofurantoin across the mammary epithelium in vivo, J. Pharmacol. Exp. Ther. 280 (1997) 664–668.
[8] V.S. Toddywalla, F.W. Kari, M.C. Neville, Active transport of nitrofurantoin across a mouse mammary epithelial monolayer, J. Pharmacol. Exp. Ther. 280 (1997) 669–676.
[9] P.O. Anderson, Drug use during breast-feeding, Clin. Pharm. 10 (1991) 594–624.
[10] S. Kacew, Adverse effects of drugs and chemicals in breast milk on the nursing infant, J. Clin. Pharmacol. 33 (1993) 213–221.
[11] J.T. Wilson, Drugs in Breast Milk, ADIS Press, Sydney, 1981.
[12] H.C. Atkinson, E.J. Begg, Clin. Pharmacokin. 18 (1990) 151.
[13] S. Agatonovic-Kustrin, G. Tucker, M. Zecevic, L.J. Zivanovic, Prediction of drug transfer into human milk based on molecular structure descriptors, Anal. Chim. Acta 418 (2000) 181–195.
[14] J.C. Dearden, Partitioning and lipophilicity in quantitative structure–activity relationships, Environ. Health Perspect. 61 (1985) 203–228.
[15] M.R. Riazi, C.H. Whitson, Estimating diffusion-coefficients of dense fluids, Ind. Eng. Chem. Res. 32 (1993) 3081–3088.

[16] A. Leo, C. Hansch, C. Church, Comparison of parameters currently used in the study of structure–activity relationships, J. Med. Chem. 12 (1969) 766–771.
[17] G. Grassy, B. Calas, A. Yasri, R. Lahana, J. Woo, S. Iyer, M. Kaczorek, R. Floc'h, R. Buelow, Computer-assisted rational design of immunosuppressive compounds, Nat. Biotechnol. 16 (1998) 748–752.
[18] D. Gorse, A. Rees, M. Kaczorek, R. Lahana, Molecular diversity and its analysis, Drug Discov. Today 4 (1999) 257–264.
[19] V.K. Gombar, D.V.S. Jain, Quantification of molecular shape and its correlation with physico-chemical properties, Indian J. Chem. 26A (1987) 554–555.
[20] E. Estrada, Generalization of topological indices, Chem. Phys. Letts. 336 (2001) 248–252.
[21] L.B. Kier, L.H. Hall, Molecular Connectivity in Structure–Activity Analysis, Research Studies Press, Willey, Letchworth, UK, 1986.
[22] A. Verloop, W. Hoogenstraaten, J. Tysker, in: E.J. Ariens (Ed.), Drug Design, vol. 7, Academic Press, New York, 1976.
[23] Z.N. Stowe, M.J. Owens, J.C. Landry, C.D. Kilts, T. Ely, A. Llewellyn, C.B. Nemeroff, Sertraline and desmethylsertraline in human breast milk and nursing infants, Am. J. Psychiatry 154 (1997) 1255–1260.
[24] L.L. Altshuler, V.K. Burt, M. McMullen, V. Hendrick, Breastfeeding and sertraline: a 24-hour analysis, J. Clin. Psychiatry 56 (1995) 243–245.
[25] P.O. Anderson, Alcohol and breastfeeding, J. Hum. Lact. 11 (1995) 321–323.
[26] R.A. Lawrence, Breastfeeding: A Guide for the Medical Profession, Mosby, St. Louis, 1994.
[27] J.C. Fleishaker, N. Desai, P.J. McNamara, Possible effect of lactational period on the milk-to-plasma drug concentration ratio in lactating women: results of an in vitro evaluation, J. Pharm. Sci. 78 (1989) 137–141.
[28] V.S. Toddywalla, S.B. Patel, S.S. Betrabet, Can chronic maternal drug therapy alter the nursing infant's hepatic drug metabolizing enzyme pattern?, J. Clin. Pharmacol. 35 (1995) 1025–1029.
[29] A. Taddio, J. Klein, G. Koren, Acyclovir excretion in human breast milk, Br. J. Clin. Pharmacol. 38 (1994) 99–102.
[30] K. Bork, T. Kaiser, P. Benes, Transfer of aciclovir from plasma to human breast milk, Arzneim.-Forsch. 50 (2000) 656–658.
[31] K.L. Wisner, J.M. Perel, R.L. Findling, Antidepressant treatment during breast-feeding. Review, Am. J. Psychiatry 153 (1996) 1132–1137.
[32] U. Breyer-Pfaff, K. Nill, K.N. Entenmann, H.J. Gaertner, Secretion of amitriptyline and metabolites into breast milk, Am. J. Psychiatry 152 (1995) 812–813.
[33] T.F. Bader, K. Newman, Amitriptyline in human breast milk and nursing infant's serum, Am. J. Psychiatry 137 (1980) 855–856.
[34] W.B. Pittard, W. O'Neal Jr, Amitriptyline excretion in human milk, J. Clin. Psychopharmacol. 6 (1986) 383–384.
[35] H. Nau, Clinical pharmacokinetics in pregnancy and perinatology. II. Penicillins. Review, Dev. Pharmacol. Ther. 10 (1987) 174–198.
[36] E. Steiner, T. Villen, M. Hallberg, A. Rane, Amphetamine secretion in breast milk, Eur. J. Clin. Pharmacol. 27 (1984) 123–124.
[37] P.E. Branebjerg, L. Heisterberg, Blood and milk concentrations of ampicillin in mothers treated with pivampicillin and in their infants, J. Perinat. Med. 15 (1987) 555–558.
[38] R.M. Welch, J.W. Findlay, Excretion of drugs in human breast milk, Drug Metab. Rev. 12 (1981) 261–277.
[39] S.H. Erickson, G.L. Oppenheim, Aspirin in breast milk, J. Fam. Pract. 8 (1979) 189–190.
[40] F. Jamali, E. Keshavarz, Salicylate excretion in breast milk, Int. J. Pharm. 8 (1981) 285–290.
[41] K.F. Ilett, Drug distribution in human milk, Aust. Prescr. 20 (1997) 35–40.
[42] W.B. White, J.W. Andreoli, S.H. Wong, R.D. Cohn, Atenolol in human plasma and breast milk, Obstet. Gynecol. 63 (1984) 42S–44S.
[43] H. Liedholm, A. Melander, P.O. Bitzen, Accumulation of atenolol and metoprolol in human breast milk, Eur. J. Clin. Pharmacol. 20 (1981) 229–231.
[44] D. Ortega, X. Viviand, A.M. Lorec, M. Gamerre, C. Martin, B. Bruguerolle, Excretion of lidocaine and bupivacaine in breast milk following epidural anesthesia for cesarean delivery, Acta Anaesthesiol. Scand. 43 (1999) 394–397.
[45] G.G. Briggs, J.H. Samson, P.J. Ambrose, D.H. Schroeder, Excretion of bupropion in breast milk, Ann. Pharmacother. 27 (1993) 431–433.
[46] E.E. Tyrala, W.E. Dodson, Caffeine secretion into breast milk, Arch. Dis. Child. 54 (1979) 787–800.
[47] J.E. Ryu, Caffeine in human milk and in serum of breast-fed infants, Dev. Pharmacol. Ther. 8 (1985) 329–337.
[48] M. Perez-Reyes, M.E. Wall, Presence of delta9-tetrahydrocannabinol in human milk, New Engl. J. Med. 307 (1982) 819–820.
[49] R. Shimoyama, T. Ohkubo, K. Sugawara, Monitoring of carbamazepine and carbamazepine 10,11-epoxide in breast milk and plasma by high-performance liquid chromatography, Ann. Clin. Biochem. 37 (Part 2) (2000) 210–215.
[50] S. Pynnonen, J. Kanto, M. Sillanpaa, R. Erkkola, Carbamazepine: placental transport, tissue concentrations in foetus and newborn, and level in milk, Acta Pharmacol. Toxicol. (Copenhagen) 41 (1977) 244–253.
[51] S. Matsuda, Transfer of antibiotics into maternal milk, Biol. Res. Pregnancy Perinatol. 5 (1984) 57–60.
[52] A. Scott, S. Forsyth, Breast feeding and antibiotics, Rev. Mod. Midwife 6 (1996) 14–16.
[53] W.J. Novick Jr, Levels of cefotaxime in body fluids and tissues: a review, Rev. Infect. Dis. 4 (1982) S346–S353.
[54] A. Dresse, R. Lambotte, M. Dubois, D. Delapierre, R. Kramp, Transmammary passage of cefoxitin: additional results, J. Clin. Pharmacol. 23 (1983) 438–440.

[55] P. Bourget, V. Quinquis-Desmaris, H. Fernandez, Ceftriaxone distribution and protein binding between maternal blood and milk postpartum, Ann. Pharmacother. 27 (1993) 294–297.
[56] D.A. Kafetzis, C.A. Siafas, P.A. Georgakopoulos, C.J. Papadatos, Passage of cephalosporins and amoxicillin into the breast milk, Acta Paediatr. Scand. 70 (1981) 285–288.
[57] J. Havelka, M. Hejzlar, V. Popov, D. Viktorinova, J. Prochazka, Excretion of chloramphenicol in human milk, J. Chemother. 13 (1968) 204–211.
[58] I. Matheson, A. Evang, K.F. Overo, Presence of chlorprothixene and its metabolites in breast milk, Eur. J. Clin. Pharmacol. 27 (1984) 611–613.
[59] P.J. McNamara, D. Burgio, S.D. Yoo, Pharmacokinetics of cimetidine during lactation: species differences in cimetidine transport into rat and rabbit milk, J. Pharmacol. Exp. Ther. 261 (1992) 918–923.
[60] A. Somogyi, R. Gugler, Cimetidine excretion into breast milk, Br. J. Clin. Pharmacol. 7 (1979) 627–629.
[61] C.Y. Oo, R.J. Kuhn, N. Desai, P.J. McNamara, Active transport of cimetidine into human milk, Clin. Pharmacol. Ther. 58 (1995) 548–555.
[62] D.K. Gardner, S.G. Gabbe, C. Harter, Simultaneous concentrations of ciprofloxacin in breast milk and in serum in mother and breast-fed infant, Clin. Pharm. 11 (1992) 352–354.
[63] J. Rampono, J.H. Kristensen, L.P. Hackett, M. Paech, R. Kohan, K.F. Ilett, Citalopram and demethylcitalopram in human milk; distribution, excretion and effects in breast fed infants, Br. J. Clin. Pharmacol. 50 (2000) 263–268.
[64] I. Matheson, K. Kristensen, P.K. Lunde, Drug utilization in breast-feeding women, Eur. J. Clin. Pharmacol. 38 (1990) 453–459.
[65] K.L. Wisner, J.M. Perel, J.P. Foglia, Serum clomipramine and metabolite levels in four nursing mother–infant pairs, J. Clin. Psychiatry 56 (1995) 17–20.
[66] J.B. Fisher, B.E. Edgren, M.C. Mammel, et al., Neonatal apnea associated with maternal clonazepam therapy: a case report, Obstet. Gynecol. 66 (Suppl. 3) (1985) S34–S35.
[67] P. Söderman, I. Matheson, Clonazepam in breast milk, Eur. J. Pediatr. 147 (1988) 212–213.
[68] C. Barnas, A. Bergant, M. Hummer, A. Saria, W.W. Fleischhacker, Clozapine concentrations in maternal and fetal plasma, amniotic fluid, and breast milk, Am. J. Psychiatry 151 (1994) 945.
[69] R.G. Meny, E.G. Naumburg, L.S. Alger, J.L. Brill-Miller, S. Brown, Codeine and the breastfed neonate, J. Hum. Lact. 9 (1993) 237–240.
[70] W. Luck, H. Nau, Nicotine and cotinine concentrations in serum and milk of nursing mothers, Br. J. Clin. Pharmacol. 18 (1984) 9–15.
[71] J. Hilbert, E. Radwanski, M.B. Affrime, G. Perentesis, S. Symchowicz, N. Zampaglione, Excretion of loratadine in human breast milk, J. Clin. Pharmacol. 28 (1988) 234–239.
[72] H.C. Stancer, K.L. Reed, Desipramine and 2-hydroxydesipramine in human breast milk and the nursing infant's serum, Am. J. Psychiatry 143 (1986) 1597–1600.
[73] R. Sovner, P. Orsulak, Excretion of imipramine and desipramine in human breast milk, Am. J. Psychiatry 136 (1979) 451–452.
[74] J. Kemp, K.F. Ilett, J. Booth, L.P. Hackett, Excretion of doxepin and *N*-desmethyldoxepin in human milk, Br. J. Clin. Pharmacol. 20 (1985) 497–499.
[75] T. Stebler, T.W. Guentert, Studies on the excretion of diazepam and nordazepam into milk for the prediction of milk-to-plasma drug concentration ratios, Pharm. Res. 9 (1992) 1299–1305.
[76] L.J. Dusci, S.M. Good, R.W. Hall, K.F. Ilett, Excretion of diazepam and its metabolites in human milk during withdrawal from combination high dose diazepam and oxazepam, Br. J. Clin. Pharmacol. 29 (1990) 123–126.
[77] M. Okada, H. Inoue, Y. Nakamura, M. Kishimoto, T. Suzuki, Excretion of diltiazem in human milk, New Engl. J. Med. 312 (1985) 992–993.
[78] D. MacKintosh, N. Buchanan, Excretion of disopyramide in human breast milk, Br. J. Clin. Pharmacol. 19 (1985) 856–857.
[79] D.B. Barnett, S.A. Hudson, A. McBurney, Disopyramide and its *N*-monodesalkyl metabolite in breast milk, Br. J. Clin. Pharmacol. 14 (1982) 310–312.
[80] K.F. Ilett, T.H. Lebedevs, R.E. Wojnar-Horton, P. Yapp, M.J. Roberts, L.J. Dusci, L.P. Hackett, The excretion of dothiepin and its primary metabolites in breast milk, Br. J. Clin. Pharmacol. 33 (1992) 635–639.
[81] Y.A. Kesaniemi, Ethanol and acetaldehyde in the milk and peripheral blood of lactating women after ethanol administration, J. Obstet. Gynaecol. Br. Commonw. 81 (1974) 84–86.
[82] J.A. Mennella, G.K. Beauchamp, Transfer of alcohol to human milk, New Engl. J. Med. 325 (1991) 981–985.
[83] J.R. Koup, J.Q. Rose, M.E. Cohen, Ethosuximide pharmacokinetics in a pregnant patient and her newborn, Epilepsia 19 (1978) 535–539.
[84] A. Rane, R. Tunell, Ethosuximide in human milk and in plasma of a mother and her nursed infant, Br. J. Clin. Pharmacol. 12 (1981) 855–858.
[85] K.F. Illet, Drug distribution in human milk, Aust. Prescr. 20 (1997) 35–40.
[86] J.H. Kristensen, K.F. Ilett, L.P. Hackett, P. Yapp, M. Paech, E.J. Begg, Distribution and excretion of fluoxetine and norfluoxetine in human milk, Br. J. Clin. Pharmacol. 48 (1999) 521–527.
[87] M. Celiloglu, S. Celiker, H. Guven, Y. Tuncok, N. Demir, O. Erten, Gentamicin excretion and uptake from breast milk by nursing infants, Obstet. Gynecol. 84 (1994) 263–265.
[88] L.J. Whalley, P.G. Blain, J.K. Prime, Haloperidol secreted in breast milk, Br. Med. J. 282 (1981) 1746–1747.

[89] R.B. Stewart, B. Karas, P.K. Springer, Haloperidol excretion in human milk, Am. J. Psychiatry 137 (1980) 849–850.
[90] K. Walter, C. Dilger, Ibuprofen in human milk, Br. J. Clin. Pharmacol. 44 (1997) 211–212.
[91] N.M. Davies, Clinical pharmacokinetics of ibuprofen. The first 30 years, Rev. Clin. Pharmacokinet. 34 (1998) 101–154.
[92] T.H. Lebedevs, R.E. Wojnar-Horton, P. Yapp, M.J. Roberts, L.J. Dusci, L.P. Hackett, K.F. Ilett, Excretion of indomethacin in breast milk, Br. J. Clin. Pharmacol. 32 (1991) 751–754.
[93] N.O. Lunell, J. Kulas, A. Rane, Transfer of labetalol into amniotic fluid and breast milk in lactating women, Eur. J. Clin. Pharmacol. 28 (1985) 597–599.
[94] T. Tomson, I. Ohman, S. Vitols, Lamotrigine in pregnancy and lactation: a case report, Epilepsia 38 (1997) 1039–1041.
[95] R.J. Summerfield, M.S. Nielsen, Excretion of lorazepam into breast milk, Br. J. Anaesth. 57 (1985) 1042–1043.
[96] P.R. Hannon, A.K. Duggan, J.R. Serwint, J.W. Vogelhut, F. Witter, C. DeAngelis, The influence of medroxyprogesterone on the duration of breast-feeding in mothers in an urban community, Arch. Pediatr. Adolesc. Med. 151 (1997) 490–496.
[97] M.D. Edstein, J.R. Veenendaal, R. Hyslop, Excretion of mefloquine in human breast milk, Chemotherapy 34 (1988) 165–169.
[98] W. Krause, I. Stoppelli, S. Milia, E. Rainer, Transfer of mepindolol to newborns by breast-feeding mothers after single and repeated daily doses, Eur. J. Clin. Pharmacol. 22 (1982) 53–55.
[99] R.E. Wojnarhorton, J.H. Kristensen, P. Yapp, F. Ilett, L.J. Dusci, L.P. Hackett, Methadone distribution and excretion into breast milk of clients in a methadone maintenance programe, Br. J. Clin. Pharmacol. 44 (1997) 543–547.
[100] B. Geraghty, E.A. Graham, B. Logan, E.L. Weiss, Methadone levels in breast milk, J. Hum. Lact. 13 (1997) 227–230.
[101] D.G. Johns, L.D. Rutherford, P.C. Leighton, C.L. Vogel, Secretion of methotrexate into human milk, Am. J. Obstet. Gynecol. 112 (1972) 978–980.
[102] W.B. White, J.W. Andreoli, R.D. Cohn, Alpha-methyldopa disposition in mothers with hypertension and in their breast-fed infants, Clin. Pharmacol. Ther. 37 (1985) 387–390.
[103] J. Kulas, N.O. Lunell, U. Rosing, B. Steen, A. Rane, Atenolol and metoprolol. A comparison of their excretion into human breast milk, Acta Obstet. Gynecol. Scand. Suppl. 118 (1984) 65–69.
[104] S.H. Erickson, G.L. Oppenheim, G.H. Smith, Metronidazole in breast milk, Obstet. Gynecol. 57 (1981) 48–50.
[105] L. Heisterberg, P.E. Branebjerg, Blood and milk concentrations of metronidazole in mothers and infants, J. Perinat. Med. 11 (1983) 114–120.
[106] C.M. Passmore, J.C. McElnay, E.A. Rainey, P.F. D'Arcy, Metronidazole excretion in human milk and its effect on the suckling neonate, Br. J. Clin. Pharmacol. 26 (1988) 45–51.
[107] A.M. Lewis, L. Patel, A. Johnston, P. Turner, Mexiletine in human blood and breast milk, Postgrad. Med. J. 57 (1981) 546–547.
[108] A. Valdivieso, G. Valdes, T.E. Spiro, R.L. Westerman, Minoxidil in breast milk, Ann. Intern. Med. 102 (1985) 135.
[109] A. Buist, L. Dennerstein, K.P. Maguire, T.P. Norman, Plasma and human milk concentrations of moclobemide in nursing mothers, Hum. Psychopharmacol. 13 (1998) 579–582.
[110] W.G. Terwilliger, R.A. Hatcher, The elimination of morphine and quinine in human milk, Surg. Gynecol. Obstet. 58 (1934) 823–826.
[111] I. Robieux, G. Koren, H. Vandenbergh, J. Schneiderman, Morphine excretion in breast milk and resultant exposure of a nursing infant, J. Toxicol. Clin. Toxicol. 28 (1990) 365–370.
[112] R.G. Devlin, K.L. Duchin, P.M. Fleiss, Nadolol in human serum and breast milk, Br. J. Clin. Pharmacol. 12 (1981) 393–396.
[113] J.H. Kristensen, K.F. Ilett, L.J. Dusci, L.P. Hackett, P. Yapp, R.E. Wojnar-Horton, M.J. Roberts, M. Paech, Distribution and excretion of sertraline and *N*-desmethylsertraline in human milk, Br. J. Clin. Pharmacol. 45 (1998) 453–457.
[114] D.T. Liu, J.M. Savage, D. Donnell, Nefopam excretion in human milk, Br. J. Clin. Pharmacol. 23 (1987) 99–101.
[115] B.B. Ferguson, D.J. Wilson, W. Schaffner, Determination of nicotine concentrations in human milk, Am. J. Dis. Child. 130 (1976) 837–839.
[116] W.B. White, S.C. Yeh, G.J. Krol, Nitrendipine in human plasma and breast milk, Eur. J. Clin. Pharmacol. 36 (1989) 531–544.
[117] G. Pons, E. Rey, M.O. Richard, F. Vauzelle, C. Francoual, C. Moran, P. d'Athis, J. Badoual, G. Olive, Nitrofurantoin excretion in human milk, Dev. Pharmacol. Ther. 14 (1990) 148–152.
[118] K.L. Wisner, J.M. Perel, Nortriptyline treatment of breast-feeding women, Am. J. Psychiatry 153 (1996) 295.
[119] K.L. Wisner, J.M. Perel, Serum nortriptyline levels in nursing mothers and their infants, Am. J. Psychiatry 148 (1991) 1234–1236.
[120] B. Olsson, P. Bolme, B. Dahlstrom, C. Marcus, Excretion of noscapine in human breast milk, Eur. J. Clin. Pharmacol. 30 (1986) 213–215.
[121] K.F. Ilett, L.P. Hackett, L.J. Dusci, M.J. Roberts, J.H. Kristensen, M. Paech, A. Groves, P. Yapp, Distribution and excretion of venlafaxine and *O*-desmethylvenlafaxine in human milk, Br. J. Clin. Pharmacol. 45 (1998) 459–462.
[122] L.J. Dusci, S.M. Good, R.W. Hall, K.F. Ilett, Excretion of diazepam and its metabolites in human milk during

withdrawal from combination high dose diazepam and oxazepam, Br. J. Clin. Pharmacol. 29 (1990) 123–126.
[123] M. Wretlind, Excretion of oxazepam in breast milk, Eur. J. Clin. Pharmacol. 33 (1987) 209–210.
[124] J. Fidler, V. Smith, M. De Swiet, Excretion of oxprenolol and timolol in breast milk, Br. J. Obstet. Gynaecol. 90 (1983) 961–965.
[125] C.M. Berlin Jr, S.J. Yaffe, M. Ragni, Disposition of acetaminophen in milk, saliva, and plasma of lactating women, Pediatr. Pharmacol. 1 (1980) 135–141.
[126] P.O. Bitzen, B. Gustafsson, K.G. Jostell, A. Melander, E. Wahlin-Boll, Excretion of paracetamol in human breast milk, Eur. J. Clin. Pharmacol. 20 (1981) 123–125.
[127] Z.N. Stowe, L.S. Cohen, A. Hostetter, J.C. Ritchie, M.J. Owens, C.B. Nemeroff, Paroxetine in human breast milk and nursing infants, Am. J. Psychiatry 157 (2000) 185–189.
[128] R. Ohman, S. Hagg, L. Carleborg, O. Spigset, Excretion of paroxetine into breast milk, J. Clin. Psychiatry 60 (1999) 519–523.
[129] E.J. Begg, S.B. Duffull, D.A. Saunders, R.C. Buttimore, K.F. Ilett, L.P. Hackett, P. Yapp, D.A. Wilson, Paroxetine in human milk, Br. J. Clin. Pharmacol. 48 (1999) 142–147.
[130] A.M. Schadewinkel-Scherkl, F. Rasmussen, C.C. Merck, P. Nielsen, H.H. Frey, Active transport of benzylpenicillin across the blood–milk barrier, Pharmacol. Toxicol. 73 (1993) 14–19.
[131] O.V. Olesen, U. Barteles, J.H. Poulsen, Perphenazine in breast milk and serum, Am. J. Psychiatry 147 (1990) 1378–1379.
[132] J.W. Findlay, R.J. DeAngelis, M.F. Kearney, R.M. Welch, J.M. Findlay, Analgesic drugs in breast milk and plasma, Clin. Pharmacol. Ther. 29 (1981) 625–633.
[133] W. Kuhnz, S. Koch, H. Helge, H. Nau, Primidone and phenobarbital during lactation period in epileptic women: total and free drug serum levels in the nursed infants and their effects on neonatal behavior, Dev. Pharmacol. Ther. 11 (1988) 147–154.
[134] J.C. Fleishaker, N. Desai, P.J. McNamara, Factors affecting the milk-to-plasma drug concentration ratio in lactating women: physical interactions with protein and fat, J. Pharm. Sci. 76 (1987) 189–193.
[135] B. Steen, A. Rane, G. Lonnerholm, O. Falk, C.E. Elwin, F. Sjoqvist, Phenytoin excretion in human breast milk and plasma levels in nursed infants, Ther. Drug Monit. 4 (1982) 331–334.
[136] P.A. Greenberger, Y.K. Odeh, M.C. Frederiksen, A.J. Atkinson Jr, Pharmacokinetics of prednisolone transfer to breast milk, Clin. Pharmacol. Ther. 53 (1993) 324–328.
[137] F.H. Katz, B.R. Duncan, Entry of prednisone into human milk, New Engl. J. Med. 293 (1975) 1154.
[138] W.B. Pittard III, H. Glazier, Procainamide excretion in human milk, J. Pediatr. 102 (1983) 631–633.
[139] P.O. Anderson, Propranolol in breast milk, Am. J. Psychiatry 136 (1979) 466.
[140] J.P. Bauer, B. Pape, J. Zajicek, T. Groshong, Propranolol in human plasma and breast milk, Am. J. Cardiol. 43 (1979) 860–862.
[141] J.M. Hilbert, R.P. Gural, S. Symchowicz, N. Zampaglione, Excretion of quazepam into human breast milk, J. Clin. Pharmacol. 24 (1984) 457–462.
[142] E.J. Begg, R.A. Robson, S.J. Gardiner, L.J. Hudson, P.A. Reece, S.C. Olson, E.L. Posvar, A.J. Sedman, Quinapril and its metabolite quinaprilat in human milk, Br. J. Clin. Pharmacol. 51 (2001) 478–481.
[143] G.P. Stoehr, R.P. Juhl, J. Veals, S. Symchowicz, R. Gural, C. Lin, R.H. McDonald, The excretion of rosaramicin in breast milk, J. Clin. Pharmacol. 25 (1985) 89–94.
[144] H.B. Lassman, S.K. Puri, I. Ho, R. Sabo, M.J. Mezzino, Pharmacokinetics of roxithromycin, J. Clin. Pharmacol. 28 (1988) 141–152.
[145] M.F. O'Hare, G.A. Murnaghan, C.J. Russell, W.J. Leahey, M.P. Varma, D.G. McDevitt, Sotalol as a hypotensive agent in pregnancy, Br. J. Obstet. Gynaecol. 87 (1980) 814–820.
[146] L.P. Hackett, R. e. Wojnar-Horton, L.J. Dusci, K.F. Ilett, M.J. Roberts, Excretion of sotalol in breast milk, Br. J. Clin. Pharmacol. 29 (1990) 277–278.
[147] C.N. Epperson, G.M. Anderson, C.J. McDougle, Sertraline and breast-feeding, New Engl. J. Med. 336 (1997) 1189–1190.
[148] S. Dodd, A. Stocky, A. Buist, C.D. Burrows, K. Maguire, T.R. Norman, Sertraline in paired blood plasma and breast-milk samples from nursing mothers, Hum. Psychopharmacol. 15 (2000) 261–264.
[149] R.E. Wojnar-Horton, L.P. Hackett, P. Yapp, L.J. Dusci, M. Paech, K.F. Ilett, Distribution and excretion of sumatriptan in human milk, Br. J. Clin. Pharmacol. 41 (1996) 217–221.
[150] P. Chaiken, M. Chasin, B. Kennedy, B.K. Silverman, Suprofen concentrations in human breast milk, J. Clin. Pharmacol. 23 (1983) 385–390.
[151] T.H. Lebedevs, R.E. Wojnarhorton, P. Yap, Excretion of temazepam in breast milk, Br. J. Clin. Pharmacol. 33 (1992) 204–206.
[152] B.H. Resman, P. Blumenthal, W.J. Jusko, Breast milk distribution of theobromine from chocolate, J. Pediatr. 91 (1977) 477–480.
[153] A.M. Yurchak, W.J. Jusko, Theophylline secretion into breast milk, Pediatrics 57 (1976) 518–520.
[154] D. Hartmann, N.O. Lunell, G. Friedrich, A. Rane, Excretion of tiapamil in breast milk, Br. J. Clin. Pharmacol. 26 (1988) 183–618.
[155] G.R. Evaldson, S. Lindgren, C.E. Nord, A.T. Rane, Tinidazole milk excretion and pharmacokinetics in lactating women, Br. J. Clin. Pharmacol. 19 (1985) 503–507.
[156] R. Sagranes, E.S. Waller, H.R. Goehrs, Tolmetin in breast milk, Drug Intell. Clin. Pharm. 19 (1985) 55–56.
[157] J.W. Findlay, R.F. Butz, J.M. Sailstad, J.T. Warren, R.M. Welch, Pseudoephedrine and triprolidine in

plasma and breast milk of nursing mothers, Br. J. Clin. Pharmacol. 18 (1984) 901–906.
[158] G.E. von Unruh, W. Froescher, F. Hoffman, M. Niesen, Valproic acid in breast milk: how much is really there?, Ther. Drug Monit. 6 (1984) 272–276.
[159] P. Anderson, U. Bondesson, I. Mattiasson, B.W. Johansson, Verapamil and norverapamil in plasma and breast milk during breast feeding, Eur. J. Clin. Pharmacol. 31 (1987) 625–627.
[160] A. Tran, T. O'Mahoney, E. Rey, J. Mai, J.P. Mumford, G. Olive, Vigabatrin: placental transfer in vivo and excretion into breast milk of the enantiomers, Br. J. Clin. Pharmacol. 45 (1998) 409–411.
[161] G. Pons, C. Francoual, P. Guillet, C. Moran, P. Hermann, G. Bianchetti, J.F. Thiercelin, J.P. Thenot, G. Olive, Zolpidem excretion in breast milk, Eur. J. Clin. Pharmacol. 37 (1989) 245–248.
[162] R. Shimoyama, T. Ohkubo, K. Sugawara, Monitoring of zonisamide in human breast milk and maternal plasma by solid-phase extraction HPLC method, Biomed. Chromatogr. 13 (1999) 370–372.
[163] I. Matheson, H.A. Sande, J. Gaillot, The excretion of zopiclone into breast milk, Br. J. Clin. Pharmacol. 30 (1990) 267–271.