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Prediction of drug loss from PVC infusion bags

H. C. ATKINSON, S. B. DUFFULL, *Department of Clinical Pharmacology, Christchurch Hospital, Private Bag, Christchurch, New Zealand*

Abstract—PVC: water partition coefficients for a series of 13 drugs have been calculated from literature data and a high degree of correlation with octanol: water partition coefficients demonstrated. The resulting model, log $P_{PVC} = -0.35 + 0.69$ log P, ($r^2 = 0.88$) has been prospectively tested with 10 drugs. All the test drugs were within the 95% confidence intervals associated with predicted log P_{PVC} values consistent with a valid model. In practice, predicted log P_{PVC} values may be used to estimate drug loss from the aqueous phase of PVC bags at equilibrium. Equations are described which enable calculation of likely drug loss from 100, 500 and 1000 mL PVC bags. It is recommended that this approach is used to identify drugs which are unlikely to be significantly absorbed into PVC.

The loss of some drugs from aqueous solutions stored in PVC bags has been well documented (Moorhatch & Chiou 1974; Cossum & Roberts 1981; Kowaluk et al 1981; Illum et al 1983; Nation et al 1983). Illum et al (1983) suggests that octanol: water partition coefficients can be used to predict sorption behaviour. In this study a predictive model is developed to estimate the sorption of any drug into PVC bags from literature data.

Materials and methods

Chemicals. The following drugs were used in the study: clonazepam (Roche, Switzerland), diclofenac (Ciba Geigy, Switzerland), flunitrazepam (Roche), fluphenazine (Squibb, USA), medazepam (Roche), naproxen (Sigma), nitrazepam (Roche), oxazepam (Wyeth & Brother, UK), phenobarbitone and promethazine (May & Baker, UK) and verapamil (Sigma).

Partition coefficients. Apparent octanol: water partition coefficient (P_{APP}) values were obtained from the literature (Tables 1, 2). Where necessary these were converted to the partition coefficient value for the un-ionized species using the equation described by Hansch (1973).

The partition coefficients between the PVC and aqueous phases, P_{PVC}, were obtained from the literature (Roberts et al 1980; Illum & Bundgaard 1982; Illum et al 1983). P_{PVC} values for clonazepam, medazepam, nitrazepam and oxazepam were calculated from literature data (Kowaluk et al 1981; Nation et al 1983) following measurement of pH at their respective equilibrium concentrations.

Measurement of partition coefficients. Drug loss from PVC bags was determined as described by Kowaluk et al (1981). The optical absorbance of samples (concentration < 30 mg L^{-1}) withdrawn at appropriate times was measured at the wavelength of maximum absorbance (Unicam SP1700 spectrometer) until equilibrium was reached. The drug loss for promethazine was remeasured at a pH value (pH = 6·00) intermediate to those in the original study by Kowaluk et al (1981), since the calculated P_{PVC} values differed by more than 1 order of magnitude.

The P_{PVC} value was calculated from:

$$P_{PVC} = \frac{(A_{std} - A_{aq})}{A_{aq}} \times \frac{V_{aq}}{V_{PVC}} \quad (1)$$

where A_{std} and A_{aq} are the absorbances of the aqueous standard and the aqueous solution in the PVC bag at equilibrium and V_{aq} and V_{PVC} are the respective volumes of the aqueous and PVC phases. Values for absorbance were between 0·10 and 0·90. V_{PVC} and V_{aq} were determined from the difference in weight between a full and dried bag converted into units of volume using the densities of PVC and saline, 1·244 g mL^{-1} (personal communication, Travenol Laboratories, Auckland, New Zealand) and 1 g mL^{-1}, respectively.

At equilibrium the pH of the solution was measured and the calculated P_{PVC} value corrected to obtain the un-ionised partition coefficient using the equation from Hansch (1973).

Modelling. A linear regression model was developed using BMDP (Department Biomathematics, UCLA, Los Angeles) from logarithms of P and P_{PVC} values in the literature (Cossum & Roberts 1981; Illum et al 1983; Nation et al 1983) (Table 1). The model was prospectively tested with the P_{PVC} values measured in this study and literature values from Roberts et al (1980) and Illum & Bundgaard (1982) (Table 2).

The 95% confidence intervals (CI) were calculated for predicted Log P_{PVC} values (Snedecor & Cochran 1967).

$$95\%\ CI = \pm 1.01 \sqrt{\frac{1.04 + (\log P - 3.98)^2}{87.46}} \quad (2)$$

Results and discussion

The equation of best fit was:

$$\log P_{PVC} = -0.35 + 0.69 \log P \quad (3)$$

with the intercept significantly different from 0 and the slope significantly different from 1 ($P < 0.01$). A good fit resulted, with a correlation coefficient (r^2) of 0·88 (n = 25).

Correspondence: S. B. Duffull, Department of Clinical Pharmacology, Christchurch Hospital, Private Bag, Christchurch, New Zealand.

Table 1. pK_a, log P and log P_{PVC} of selected drugs.

Drug	pK_a	log P	log P_{PVC}
Lignocaine	7·9(1) B	2·00[a](2)	0·59[b](2)
Clomethiazole	3·2(2) B	2·12(2)	1·26[b](2) 1·29[b](2)
Clonazepam	1·5(1) B 10·5(1) A	2·41(3)	1·08[b,c](4)
Warfarin	5·05(1) A	2·61[d](2,5)	1·70(6) 1·80(6) 2·37[b](2)
Diltiazem	7·7(6) B	2·69(5)	1·30(6) 1·40(6)
Diazepam	3·4(1) B	2·81[d](3)	1·09[b](2) 1·15[b](2)
Hydralazine	7·1(1) B	2·91[a](2)	2·36[b](2)
Thiopentone	7·45(1) A	3·01[d](2,6)	1·18[b](2) 1·20[b](2) 1·40(6) 1·50(6)
Promethazine	9·1(1) B	5·20[d](3)	4·05[c] 4·23[b](2)
Promazine	9·4(1) B	5·32[d](3)	3·37[b](2)
Trifluoroperazine	8·1(1) B	5·97[d](3)	3·17[b](2)
Chlorpromazine	9·3(1) B	6·96[d](3)	4·11[b](2) 4·33[b](2) 4·50(6) 4·70(6)
Thioridazine	9·5(1) B	7·63[d](3)	4·43[b](2)

Footnotes: [a] Values were converted to true partition coefficient values for the un-ionised species. [b] Calculated from experimental data in the reference listed, as described in methods section. [c] Not ionised to any significant extent. [d] Mean value. [e] Measured in this study.

References: (1) Newton & Kluza (1978); (2) Kowaluk et al (1981); (3) Hansch & Leo (1979); (4) Nation et al (1983); (5) Illum et al (1983); (6) Prankerd (1984).

Log P_{PVC} values and literature values used to prospectively test the model (Table 2) were all within the 95% confidence intervals for the predictive model (Fig. 1).

V_{PVC} values (mean ± s.d., n = 12) for 100, 500 and 1000 mL bags were 13·34 ± 0·30, 19·49 ± 0·47 and 29·24 ± 0·43 mL, respectively.

Prospective testing, described by Hocking (1975), was required to validate the developed model (eqn 3). Measured and literature log P_{PVC} values (Table 2) used to prospectively test the model were all within the 95% confidence intervals associated with predicted log P_{PVC} values (Fig. 1), consistent with a valid model.

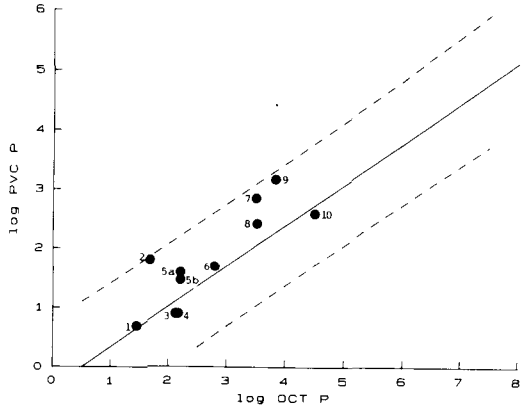

FIG. 1. Predictive model for P_{PVC}: water partition coefficients (log P_{PVC}), associated 95% confidence intervals (- - - -) and test drugs: 1, phenobarbitone; 2, flunitrazepam; 3, nitrazepam; 4, oxazepam; 5, nitroglycerin; 6, medazepam; 7, fluphenazine; 8, naproxen; 9, verapamil; 10, diclofenac.

In practice the predicted log P_{PVC} value would be used to calculate the proportion of drug likely to be lost from the aqueous phase of a PVC infusion bag. This requires calculation of drug in the PVC, and aqueous phases, f_{PVC} and f_{aq}, respectively,

$$\frac{f_{PVC}}{f_{aq}} = P_{PVC} \times (1-\alpha) \times \frac{V_{PVC}}{V_{aq}} \quad (4)$$

where α is the fraction of ionised drug calculated from the pH of the aqueous phase and the drug pKa (Hansch 1973).

The proportion of drug lost from aqueous solution may then be calculated. There is a possibility in the case of drugs appreciably absorbed that the pH of the solution will change with the changing aqueous concentration thereby affecting the fraction ionised (α) and the estimated loss. It is therefore only appropriate to use this procedure for drugs with only a small loss from solution, i.e. < 10%, as the pH of solution would be unlikely to be altered by the small change in concentration. This would be less critical for drugs which are only very weak acids or bases and are therefore essentially un-ionised. If a drug is chemically stable, the predicted fraction of drug lost into the

Table 2. pK_a, log P and predicted and observed log P_{PVC} values of selected drugs.

			logP_{PVC}	
Drug	pK_a	log P	predicted[a]	observed
Phenobarbitone	7·41(A) (1)	1·45[b](2)	0·65	0·69[c]
Flunitrazepam	1·8(B) (1)	1·68 (3)	0·81	1·81[c]
Nitrazepam	3·2(B) 10·8(A) (1)	2·12 (2)	1·11	0·9(4)
Oxazepam	1·8(B) 11·1(A) (1)	2·17 (2)	1·15	0·9(4)
Nitroglycerin	NA	2·2 (4)	1·17	1·47(5) 1·6(4)
Medazepam	4·4(B) (1)	2·79[b](2)	1·58	1·7(4)
Fluphenazine	3·90, 8·1(B) (1)	3·5 (3)	2·07	2·86[c]
Naproxen	4·15(A) (1)	3·52 (3)	2·08	2·43[c]
Verapamil	9·0(B) (6)	3·83 (3)	2·30	3·18[c]
Diclofenac	4·0(A) (7)	4·5 (3)	2·76	2·60[c]

Footnote: [a] From best fit equation 2. [b] Mean value. [c] Measured in this study.

References: (1) Newton & Kluza (1978); (2) Hansch & Leo (1979); (3) Atkinson & Begg (1988); (4) Illum & Bundgaard (1982); (5) Roberts et al (1980); (6) Inoue et al (1984); (7) Riess et al (1978).

PVC would represent the worst possible case and therefore the calculation ers on the side of safety.

The drugs in the predictive model have widely varying structures and lipophilicities spanning 5 orders of magnitude of P values. The model would therefore be able to predict unknown log P_{PVC} values for a wide range of drugs.

The model and equations developed can be used to calculate whether a drug loss of less than 10% is expected due to absorption into PVC infusion bags.

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