which describes the solubility of phenobarbital in propylene glycol–water.

When $f_1 = 0$ and f_2 is variable, Eq. 2 reduces to:

$$\log S_t = \log S_0 + \alpha_2 f_2 \qquad \text{(Eq. 5)}$$

which describes the solubility of phenobarbital in glycerol–water binary systems. Figure 3 shows the fitting of theoretical lines calculated on the basis of Eq. 2 to experimental points determined in the present study. The good fit suggests the possible use of such an equation for solubility predictions in ternary propylene glycol–glycerol–water systems.

Gorman and Hall (14) reported a linear relationship between the logarithm of secobarbital solubility and the dielectric constant of the binary solvent systems which have similar bonding characteristics: ethanol–water, glycerol–water, and propylene glycol–water. In the present investigation, the log solubility–dielectric constant (calculated) relationship for phenobarbital in propylene glycol–water and glycerol–water was also linear (Fig. 4). When this approach was extended to phenobarbital solubility in propylene glycol–glycerol–water, an essentially linear relationship was observed (Fig. 4). However, this linearity does not seem to extend to solvent systems containing high proportions of water since the line does not intersect with the other two lines at 100% water solvent composition. This result does not allow for solubility predictions over a wide range of solvent compositions as is possible when Eq. 2 is utilized.

The effect of temperature on phenobarbital solubility in 12 selected solvent systems was studied. Equilibrium solubilities were determined at 23, 32, 40, and 45 ± 0.2°, and the log solubility–$1/T$ relationships were plotted (Fig. 5). The heats of solution calculated from Fig. 5 varied in the relatively narrow range of 6–8 kcal/mole for the different solvent systems. The relatively nonpolar phenobarbital molecule is believed to dissolve in the relatively polar solvent blends through hydrogen bonding of the electronegative oxygen of the phenobarbital carbonyl groups to the hydrogen of hydroxyl groups in water, glycerol, or propylene glycol. The close values of heats of solution suggest similar types of solution mechanism and bonding.

Results of the present investigation showed that phenobarbital solubility can be effected through the use of mixed ethanol-free solvents to produce concentrations well above those required to formulate a phenobarbital elixir. The correlation of solubility data to specific solvent contributions enabled solubility predictions from a knowledge of solvent composition. Evaluation of the stability and bioavailability of phenobarbital in these solvent systems will be reported later.

REFERENCES

(1) "Evaluations of Drug Interactions," 2nd ed., American Pharmaceutical Association, Washington, D.C., 1976.

(2) G. E. Dukes, J. G. Kuhn, and R. P. Evens, *Am. Fam. Physician*, **16**, 97 (1977).

(3) N. C. Petroni and A. A. Cardoni, *Drug Ther.*, **8**, 72 (1978).

(4) G. M. Krause and J. M. Cross, *J. Am. Pharm. Assoc., Sci. Ed.*, **40**, 137 (1951).

(5) R. A. Anderson, *Austr. J. Pharm.*, **30**, 96 (1949).

(6) A. Urdang and E. E. Leuallen, *J. Am. Pharm. Assoc., Sci. Ed.*, **45**, 425 (1956).

(7) C. F. Peterson and R. E. Hopponen, *ibid.*, **42**, 540 (1953).

(8) N. C. Zacharias, *Can. Pharm. J.*, **84**, 608 (1951).

(9) T. L. Breon and A. N. Paruta, *J. Pharm. Sci.*, **59**, 1306 (1970).

(10) V. F. Naggar, M. A. Moustafa, S. A. Khalil, and M. M. Motawi, *Can. J. Pharm. Sci.*, **7**, 112 (1972).

(11) S. A. Khalil, M. A. Moustafa, V. F. Naggar, and M. M. Motawi, *ibid.*, **7**, 109 (1972).

(12) T. Higuchi and E. Brochmann-Hanssen, "Pharmaceutical Analysis," Interscience, New York, N.Y., 1961, p. 231.

(13) S. Yalkowsky, G. L. Flynn, and G. L. Amidon, *J. Pharm. Sci.*, **61**, 983 (1972).

(14) W. G. Gorman and G. D. Hall, *ibid.*, **53**, 1017 (1964).

ACKNOWLEDGMENTS

Presented at the APhA Academy of Pharmaceutical Sciences, San Antonio meeting, November 1980.

The authors thank Mr. I. D. Marlow for technical assistance.

COMMUNICATIONS

Single-Point Maintenance Dose Prediction: Role of Interindividual Differences in Clearance and Volume of Distribution in Choice of Sampling Time

Keyphrases ☐ Pharmacokinetics—single-point maintenance dose prediction, theoretical analysis ☐ Single-point maintenance dose prediction—pharmacokinetics, theoretical analysis

To the Editor:

Experimental observations of very strong correlations between a single determination of concentration after the first dose of a drug and the eventual steady-state concentration have been observed experimentally for lithium, nortriptyline, imipramine, and desipramine (1–5). Such a relationship also exists for drugs with short half-lives based on simulations and clinical studies of chloramphenicol and theophylline (6–8).

If a single determination of concentration after the first dose of drug correlates with the eventual steady-state concentration, then, over the linear range, this correlation provides the basis for the prediction of maintenance dose necessary to achieve a desired steady-state concentration. In an attempt to clarify this very powerful method of maintenance dose prediction, a theoretical analysis of the relationship was carried out to determine the: (*a*) source

0022-3549/81/1000-1174$01.00/0

and magnitude of the error involved with the estimate, (*b*) general applicability of the method to other drugs, and (*c*) limits of the method's application (9). It was observed that the method yielded a good estimate of clearance in an individual which did not seem to be affected by interindividual variation in the volume of distribution (10).

The analysis described the inverse relationship between the concentration (C^*) observed at some time (t^*) after the first dose (D^*) and the maintenance dose (D_m) required to obtain a desired steady-state drug concentration ($\overline{C}_{ss}$):

$$1/D_m = \Psi C^* \qquad \text{(Eq. 1)}$$

where:

$$\Psi = \frac{e^{Kt^*}}{\overline{C}_{ss} K \tau D^*} \qquad \text{(Eq. 2)}$$

where K is the elimination rate constant of the drug in an individual patient and τ is the dosing interval. It was previously noted (9) that Ψ (the proportionality factor in Eq. 1 as defined by Eq. 2) would vary among individuals but in such a manner that, at a certain t^*, the variability would not allow estimates of D_m that would yield $\overline{C}_{ss}$ values within 10–20% of the target value.

The purpose of this communication is to extend this analysis into areas not completely dealt with previously:

1. Since K is a function of clearance (Cl) and volume of distribution (V), how does Ψ vary as a function of interindividual variability in these independent parameters?
2. Why is Ψ relatively constant throughout a population?
3. What factors determine the optimum value of t^*?

To answer these questions, it is first necessary to recast Ψ as a function of clearance and volume of distribution through the relationship:

$$K = Cl/V \qquad \text{(Eq. 3)}$$

Therefore:

$$\Psi = \frac{V e^{(Cl/V)t^*}}{Cl \overline{C}_{ss} \tau D^*} \qquad \text{(Eq. 4)}$$

The portion of Ψ that varies among the population is $(V/Cl)e^{(Cl/V)t^*}$. Ideally, Ψ would not vary from one individual to another, but since Cl and V vary throughout the population, Ψ will vary among individuals. However, Ψ is minimally affected by interindividual differences in Cl and V when its partial first derivatives with respect to these independent variables are simultaneously close to zero. The partial first derivatives are equal to zero when:

$$(Cl/V)t^* = 1 \qquad \text{(Eq. 5)}$$

or:

$$t^* = V/Cl = 1/K \qquad \text{(Eq. 6)}$$

Thus, Ψ is insensitive to interindividual differences in Cl and V when $(Cl/V)t^*$ is in the neighborhood of 1.

It is important to remember that Ψ does not vary simply as a function of Cl or V among individuals but actually varies as a function of their ratio, K. Therefore, it is appropriate to consider the intersubject variability of Ψ as a function of K and to consider the influence of interindividual variability in K on the value of Ψ as defined by Eq. 2.

Since K varies among individuals, the true value of Ψ also varies throughout the popultion. However, under certain conditions, Ψ varies much less than K. The variability in K causes minimum fluctuations in Ψ if K and e^{Kt^*} vary in proportion to one another (Eq. 2). When the exponent (x) of e^x is in the neighborhood of 1, the value of e^x varies in rough proportion to x. As seen in Table I, a fourfold variation in x centered around 1 produces less than a 15% variation in the function e^x/x about its mean value.

Table I—Effect of Varying the Value of x about 1 on the Value of the Function e^x/x

x	e^x	e^x/x	Ratio[a]
0.50	1.65	3.30	1.01
1.25	2.79	2.79	0.86
2.00	7.39	3.69	1.13
Mean		3.26	

[a] Ratio of e^x/x for each value of x to the mean value.

Equation 2 is of the form $e^x/(x/t^*)$ where $x = (Cl/V)t^* = Kt^*$. When the value of t^* in Eq. 6 is substituted into Eq. 2, the value of the exponent is 1. When x increases, e^x increases in rough proportion, and the value of the ratio in Eq. 2 does not change greatly. Therefore, Ψ does not vary greatly with K as long as Kt^* remains in the neighborhood of 1.

In addition, from the steps leading to Eq. 6, it is seen that the value of Ψ is insensitive to interindividual changes in Cl and V when $(Cl/V)t^*$ (*i.e.*, Kt^*) is in the neighborhood of 1. Since t^* is chosen and fixed in the single-point method of maintenance dose prediction and since K varies among individuals, changes in Cl and V increasingly affect Ψ as Kt^* moves away from 1. If the influence of interindividual differences in Cl and V are to be kept at a minimum for the majority of the population and if the mathematical properties of Eq. 2 are to be taken advantage of, t^* should be chosen as the mean (or mode) value of $1/K$.

When t^* is chosen in this manner, Ψ varies minimally with changes in K and the method gives estimates of maintenance doses based on a population average value of Ψ that are minimally affected by interindividual variability in Cl and V. These considerations can be extended to any one-compartment drug for which a clinically acceptable value of t^* (perhaps not >24 hr) can be chosen such that Kt^* can be kept in the neighborhood of 1 throughout the population. This approach is presently being extended to multicompartment drugs and the prediction of steady-state concentrations of metabolites of therapeutic interest.

(1) T. B. Cooper, P.-E. E. Bergner, and G. M. Simpson, *Am. J. Psychiatry*, **130**, 601, (1973).

(2) T. B. Cooper and G. M. Simpson, *ibid.*, **133**, 440 (1976).

(3) *Ibid.*, **135**, 333 (1978).

(4) R. Braithwaite, S. Montgomery, and S. Dawling, *Clin. Pharmacol. Ther.*, **23**, 303 (1978).

(5) D. J. Brunswick, J. D. Amsterdam, J. Mendels, and S. L. Stern, *ibid.*, **25**, 605 (1979).

(6) J. R. Koup, C. M. Sack, A. L. Smith, and M. Gibaldi, *Clin. Pharmacokinet.*, **5**, 460 (1980).

(7) J. R. Koup, C. M. Sack, A. L. Smith, W. M. Neely, and M. Gibaldi, *ibid.*, **6**, 83 (1981).

(8) G. G. Shapiro, J. R. Koup, C. T. Furukawa, W. E. Pierson, M. Gibaldi, D. Fuquay, and C. W. Bierman, *Pediatrics*, in press.

(9) J. T. Slattery, M. Gibaldi, and J. R. Koup, *Clin. Pharmacokinet.*, **5**, 377 (1980).

(10) J. R. Koup, J. T. Slattery, and M. Gibaldi, *Res. Commun. Chem. Pathol. Pharmacol.*, **25**, 559 (1979).

John T. Slattery
Department of Pharmaceutics
University of Washington
Seattle, WA 98105

Received February 18, 1981.
Accepted for publication June 10, 1981.
Discussions with Dr. René Levy and Dr. Milo Gibaldi are gratefully acknowledged.

Correlation of Water Solubility with Octanol–Water Partition Coefficient

Keyphrases □ Solubility—water, correlation with octanol–water partition coefficient □ Partition coefficient—octanol–water, correlation with water solubility □ Melting-point effect—correlation between water solubility and octanol–water partition coefficient

To the Editor:

Yalkowsky and Valvani (1) made a valuable analysis of the melting-point effect on the solubility of solid compounds and discussed the correlation between water solubility (S) and the octanol–water partition coefficient (P). Regression equations between log S and log P were constructed using log P values calculated primarily from molecular fragment constants developed by Nys and Rekker (2).

We have found several points relevant to the Yalkowsky–Valvani analysis (1). First, part of their conclusions for a particular class of compounds was based on a linear regression between the values of log S_{obs} and log P_{estim} obtained from the correlation equation for that class of compounds. Regression of this kind must, in principle, yield log S_{obs} = 1.0 log S_{estim} with an intercept equal to 0.0. The correlation coefficient will then be a measure of how well log S_{obs} fits log S_{estim}. For reasons unspecified, this condition was not met in their Eqs. 32–36.

Second, the calculated values of log P for some low solubility compounds are highly imprecise. For instance, the values of log P, 5.05, 5.79, and 6.53, estimated for 1,2,3,5-tetra-, penta-, and hexachlorobenzene, respectively, in their Table VI, are considerably greater than the corresponding experimental values of 4.46 (3), 4.94 (3), and 5.50 (4). It is surprising that the molar solubilities (log S) predicted from these calculated log P values and the solute melting points (MP) fall into close agreement with the experimental log S. If experimental log P values are entered into the correlation derived by Yalkowsky *et al.* (5) for the compounds in Table VI, *i.e.*, log $S = -0.9874 \log P - 0.0095(MP) + 0.7178$, the estimated S values then deviate appreciably from the experimental data.

It is understood that log P values calculated by various fragment approaches are only as accurate as the values used to define each fragment. At this time, the rules to calculate log P values are empirically derived. This approach has led to numerous correction factors for such things as branching, flexibility, chain length, bond unsaturation, and substituent polarity. In general, the fragment approach works reasonably well for simple low molecular weight molecules. It tends to be less accurate for more complex molecules.

Third, Yalkowsky and Valvani assumed that the effect of octanol–water mutual saturation on the partition coefficient was small and thus ignored it in their treatment. Banerjee *et al.* (3) also reported no observable effect of octanol–water mutual saturation. Although this effect is expected to be small for compounds with relatively high solubilities in both octanol and water, it becomes significant for solutes with limited solubilities. Consequently, it would be a factor in the correlation of log S *versus* log P at the low S (high P) region.

The significance of octanol–water mutual saturation may be evaluated by comparing experimental P values with those calculated from solute solubilties in octanol and water for some high melting solid compounds. Because of the high melting-point effect, solids have limited solubilities in both solvents and their partition coefficients can be determined directly from the ratios of solute solubilties in the two solvents. Note that at low (mole fraction) concentrations, solute activity coefficients are essentially constant and the log P of a solute would be practically constant at all concentrations.

We selected *p,p'*-dichlorodiphenyltrichloroethane (I)[1], hexachlorobenzene (II)[2], and anthracene (III) for illustration. The experimental and estimated octanol–water partition coefficients and the determined solubilities in water, octanol, and water-saturated octanol for these compounds are given in Table I. If it is assumed that mutual saturation has no effect on solute partitioning, the partition coefficients should be equal to the ratios of solute solubilties in pure octanol and water (S_o/S_w); *i.e.*, log P = 6.88 for I, 5.85 for II, and 4.73 for III. These calculated P values are larger than the experimental values by factors of 3.3, 2.2, and 1.9 for I, II, and III, respectively. The difference between experimental and calculated P values results presumably from an alteration of the solute solubilities in the two solvents due to their mutual saturation.

Table I—Solubilities and Octanol–Water Partition Coefficients of I, II, and III

Compound	Melting Point	S_w (μg/liter)[a]	S_o (g/liter)	$S_{o/w}$ (g/liter)	log S_o/S_w	log P_{exp}	log P_{est}[b]
I	108.5°	5.5 (25°)[c] 5.0 (20°)	41.5 (24°)	31.9 (24°)	6.88	6.36	—
II	230°	5.0 (25°)[c]	3.53 (23°)	2.65 (23°)	5.85	5.50	6.53
III	216°	45 (25°)[d]	2.44 (23°)	2.22 (23°)	4.73	4.45[e]	4.63

[a] Key: S_w, solubility in water; S_o, solubility in octanol; $S_{o/w}$, solubility in water-saturated octanol; and P_{exp}, experimental octanol–water partition coefficient. [b] Estimated values from fragment constants given in Ref. 1. [c] Reference 7. [d] Reference 8. [e] Reference 6.

[1] Commonly referred to as DDT.
[2] Commonly referred to as HCB.