Individualization of phenytoin therapy

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Mullen & Foster (1979) have recently evaluated six methods for individualizing phenytoin dosage regimens based upon steady-state serum concentrations produced by two or more different dosing rates. A major assumption of their evaluation technique was that the rate of drug intake was known without error. They point out in their methods, but fail to emphasize in their discussion, that in a clinical situation the dosing rate may be quite variable. During once a day dosing one deleted or added dose in a 2 week period creates a 7% error in overall dosing rate. The technique for individualizing phenytoin regimens based on the Hofstee (1952) plot has been shown to be clinically adequate when reliable dosing rate and serum concentration data are available (Ludden et al 1976, 1977). In fact, Mullen (1978) compared the direct linear plot (Eisenthal & Cornish-Bowden 1974) with the Hofstee (1952) plot using data from Richens & Dunlop (1975). If the calculations are performed correctly (Golby 1978), the two methods yield almost identical correlation coefficients (0·993 and 0·991, respectively) for observed vs predicted serum concentrations.

As pointed out by Mullen (1978) and Mullen & Foster (1979) the direct linear plot has several practical advantages over other graphical techniques. However, in the usual clinical situation, where only two reliable steady-state serum concentrations at different dosing rates are available, all methods for estimating V_{max} and K_m values are mathematically equivalent. The problem reduces to the solving of two simultaneous equations. If R_1, C_1 and R_2, C_2 are the dosing rate, steady-state serum level data pairs, the Hofstee (1952) rearrangement of the Michalis-Menten equation yields:

$$R_1 = V_{max} - K_m \frac{R_1}{C_1} \quad .. \quad .. \quad .. \quad (1)$$

where V_{max} = the apparent maximum rate of drug elimination and K_m = the serum concentration at which the rate of elimination is half maximal

$$\text{and} \quad R_2 = V_{max} - K_m \frac{R_2}{C_2} \quad .. \quad .. \quad (2)$$

Subtracting equation (1) from equation (2) and rearranging yields

$$K_m = \frac{R_1 - R_2}{(R_2/C_2) - R_1/C_1} \quad .. \quad .. \quad (3)$$

The K_m value can then be used with either equation (1) or (2) to calculate the V_{max} value. For example:

$$V_{max} = R_2 + K_m \frac{R_2}{C_2} \quad .. \quad .. \quad (4)$$

The above calculations can be carried out in seconds using a programmable calculator, obviating the need for carrying graph paper to clinic or on rounds.

Only 5 out of over 200 pharmacokinetic consults involving phenytoin provided by our Clinical Pharmacokinetic Consult Service over the last 4 years included more than two reliable steady-state serum concentrations at different dosing rates. However, when more than two reliable data points are available then the direct linear plot, on both practical and theoretical grounds, is the preferred method for arriving at an individualized phenytoin dosage regimen. A program for use with a programmable calculator is also available for the direct linear plot (Golby 1978).

When working with minimal amounts of data as is done in serum concentration monitoring, the clinician must assure himself that the data are accurate. Mullen & Foster (1979) included up to 56·4% error in their lowest serum concentration values for their computer simulations. Low serum concentration determinations frequently have high coefficients of variation. Use of such data for any type of pharmacokinetic calculation should be avoided.

The clinician must evaluate not only assay accuracy and patient compliance but also the fraction of steady-state that a given serum concentration represents. This may be particularly difficult with phenytoin (Ludden et al 1978). Failure to use steady-state data when such are required may result in inappropriate dosage regimens regardless of the mathematical technique used.

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REFERENCES

Eisenthal, R., Cornish-Bowden, A. (1974) Biochem. J. 139: 715–720

Golby, R. L. (1978) Clin. Pharmacol. Ther. 24: 253

Hofstee, B. H. J. (1952) Science 116: 329–331

Ludden, T. M., Hawkins, D. W., Allen, J. P., Hoffman, S. F. (1976) Lancet 1: 307–308

Ludden, T. M., Allen, J. P., Valutsky, W. A., Vicuna, A. I., Nappi, J. M., Hoffman, S. F., Wallace, J. E., Lalka, D., McNay, J. L. (1977) Clin. Pharmacol. Ther. 21: 287–293

Ludden, T. M., Allen, J. P., Schneider, L. W., Stavchansky, S. A. (1978) J. Pharmacokinet. Biopharm. 6: 399–415

Mullen, P. W. (1978) Clin. Pharmacol. Ther. 23: 228–232

Mullen, P. W., Foster, P. W. (1979) J. Pharm. Pharmacol. 31: 100–104

Richens, A. Dunlop, A. (1975) Lancet 2: 247–248