1-{[(10,11-Dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5-yl)thio]acetyl}-4-methylpiperazine Methiodide (VII)—The acyl halide was prepared as previously described. To this was added 1-methylpiperazine (6.0 g., 0.06 mole) dissolved in anhydrous ether, and the mixture was allowed to react for 8 hr. Extraction of the ethereal solution with 10% sodium hydroxide (4 × 50-ml. portions) followed by 10% hydrochloric acid resulted in a gummy precipitate in the aqueous layer. The aqueous layer was made alkaline and extracted with ether; the ether was washed with distilled water (6 × 50-ml. portions) and filtered and dried over anhydrous sodium sulfate. The desired sulfide was characterized as the methiodide salt prepared by conventional methods (10), IR spectra, and analytical data.

Anal.—Calc. for $C_{23}H_{29}IN_2OS \cdot {}^1/_2H_2O$: C, 53.37; H, 5.84. Found: C, 53.75; H, 6.40.

PHARMACOLOGICAL METHODS

Compounds V and VI were administered intraperitoneally to guinea pigs 20 min. before subjecting them to atomized histamine under conditions previously described (11). Because of the low solubility of the test compounds in propylene glycol, 0.05 ml. of polysorbate 20[1] was added to each milliliter of propylene glycol. Diphenhydramine hydrochloride[2] was used as the standard.

Compound VII as the methiodide salt was tested for its spasmolytic effects on spasms induced by histamine diphosphate on isolated guinea pig ileum.

Tables I and II give the results from the preliminary pharmacological testing.

[1] Tween 20, Atlas Chemical Co., Wilmington, Del.
[2] Benadryl, Parke-Davis and Co., Detroit, Mich.

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COMMUNICATIONS

Multiple-Dose Kinetics of Pharmacological Effects of Indirect Anticoagulants

Keyphrases □ Anticoagulants (warfarin and dicumarol)—mathematical derivation of multiple-dose kinetic equations, pharmacological effects □ Pharmacokinetics, multiple-dose and pharmacological effects—calculations regarding behavior and optimal regimen for indirect anticoagulants □ Multiple-dose kinetics—pharmacological effects, indirect anticoagulants

Sir:

The pharmacological effects of hypoprothrombinemic anticoagulant drugs vary widely between individuals and preclude a predictable response to a fixed dose of these agents. A given dosage schedule may be totally inadequate to prevent thrombosis in one individual but may cause hemorrhage in another (1). In addition, the effects of the drugs can be appreciably influenced within individuals through interactions with other concurrently administered drugs (2–5). These facts, as well as a need to readjust therapeutic levels of activity during the course of therapy (1), obviously necessitate patient individualization of dosing regimens for these drugs and clearly emphasize the need for predictive interrelationships between dosage regimens and the magnitudes of their drug response. The purpose of the present communication is to describe the derivation of theoretical relationships which, provided adequate data in the form of blood coagulability and plasma drug levels are collected, could be useful for the characterization of multiple-dosing pharmacokinetic be-

havior and the computation of optimal dosing regimens for individual patients.

The present approach represents an extension of the significant contributions of Levy, O'Reilly, and coworkers (2–7) concerning the kinetics and mechanisms of hypoprothrombinemic anticoagulants. In accordance with their treatment, the synthesis rate, R_s, of prothrombin complex activity, P, is logarithmically dependent upon the plasma concentration, C_p, of anticoagulant. The relationship is given by Eq. 1:

$$R_s = -m \ln \frac{C_p}{C_{p,\max}} \qquad \text{(Eq. 1)}$$

where $C_{p,\max}$ represents the plasma level at which the synthesis rate reduces to zero and m is a constant.

The time variation of the prothrombin complex activity in the plasma, given in percent of normal, is described by the differential equation (Eq. 2) where t represents the time, and K_d symbolizes a first-order constant for the degradation of P:

$$dP/dt = -m \ln C_p/C_{p,\max} - K_d P \qquad \text{(Eq. 2)}$$

The plasma concentration, in terms of a single-compartment model, is described by Eqs. 3 and 4:

$$dC_p/dt = -K_e C_p \qquad \text{(Eq. 3)}$$

$$dC_p/dt = K_a C_0 e^{-K_a t} - K_e C_p \qquad \text{(Eq. 4)}$$

which are appropriate for intravenous and oral dosing, respectively. K_e and K_a represent first-order elimination and absorption constants, respectively; and C_0 is related to the dose, D, by $C_0 = D/V_d$, where V_d is the volume of distribution. For drugs that are highly bound to plasma proteins, *e.g.*, warfarin, V_d is of the same order of magnitude as the albumin space, *i.e.*, 2.6 times the plasma volume (7).

Equation 3 or 4 may be readily solved to obtain the time dependence of C_p following single or multiple dosing which, in turn, permits similar solutions for Eq. 2 to describe the time course of P following single or multiple dosing by intravenous or oral routes of administration. Substitution of Eq. 3 into Eq. 2 and solving will obviously produce a result that is precise for intravenous dosing; because of the large order of magnitude of the difference in the absorption and elimination constants ($K_a \gg K_e$) (2), the result will also be approximately correct for oral dosing as well. Integration of Eq. 3 yields Eq. 5; its substitution into Eq. 2 provides Eq. 6 as a description of the time variation of prothrombin complex activity following a single dose of an indirect anticoagulant drug:

$$C_p = C_p^0 e^{-K_e t} \qquad \text{(Eq. 5)}$$

$$P = 100e^{-K_d t} - \frac{mK_e}{K_d^2}(1 - K_d t - e^{-K_d t}) - \frac{m}{K_d} \ln \frac{C_p^0}{C_{p,\max}} (1 - e^{-K_d t}) \qquad \text{(Eq. 6)}$$

The first and second derivatives of Eq. 5 with respect to time are given by Eqs. 7 and 8, respectively:

$$\frac{dP}{dt} = -100K_d e^{-K_d t} + \frac{mK_e}{K_d}(1 - e^{-K_d t}) - me^{-K_d t} \ln \frac{C_p^0}{C_{p,\max}} \qquad \text{(Eq. 7)}$$

$$\frac{d^2P}{dt^2} = 100K_d^2 e^{-K_d t} + mK_e e^{-K_d t} + mK_d e^{-K_d t} \ln \frac{C_p^0}{C_{p,\max}} \qquad \text{(Eq. 8)}$$

Intersubject variations of the parameters in Eqs. 6–8 are pronounced. For two of the most commonly employed anticoagulants, warfarin and dicumarol (bishydroxycoumarin), the values of m have been reported to range from 30 to 108 and from 71 to 582, respectively (2). Appreciable variations for $C_{p,\max}$ were reported to have ranged from 2.1 to 17 and from 40 to 135, respectively, for warfarin and dicumarol. Variations in K_e and K_d are less pronounced and have values of the order of 0.1 and 1.0 days^{-1}, respectively. The variation of these kinetic parameters may obviously be assumed to be principally responsible for the wide intersubject variation in response to any given dose and the need to adjust dosages for individual patients. Following a single intravenous dose of an anticoagulant, the kinetic parameters for a given individual may be evaluated from the results of monitoring the time course of plasma drug levels and prothrombin complex activity. The drug elimination constant, K_e, may be obtained in the usual way from the slope of a semilogarithmic plot of C_p *versus* t; C_p^0 is obtained from the intercept on the ordinate. The P *versus* t data allow the graphical or numerical estimation of dP/dt and d^2P/dt^2. The degradation constant, K_d, can then be identified as the negative of the slope of a plot of $\ln (d^2P/dt^2)$ *versus* t; the intercept, A, of the plot is given by Eq. 9:

$$A = 100K_d^2 + mK_e + mK_d \ln \frac{C_p^0}{C_{p,\max}} \qquad \text{(Eq. 9)}$$

At the time, $t_{\min}$, at which P is noted to become minimal, the first derivative can be set equal to zero, *i.e.*, $(dP/dt)_{t_{\min}} = 0$, to obtain Eq. 10:

$$100K_d e^{-K_d t_{\min}} - \frac{mK_e}{K_d}(1 - e^{-K_d t_{\min}}) + me^{-K_d t_{\min}} \ln \frac{C_p^0}{C_{p,\max}} = 0 \qquad \text{(Eq. 10)}$$

Equations 9 and 10 can be solved simultaneously to obtain the two remaining constants, m and $C_{p,\max}$, as given by Eqs. 11 and 12:

$$m = \frac{A}{K_e} e^{-K_d t_{\min}} \qquad \text{(Eq. 11)}$$

$$C_{p,\max} = C_p^0 e^{-[(A - 100K_d^2 - mK_e)/mK_d]} \qquad \text{(Eq. 12)}$$

It is apparent from this treatment that C_p and P *versus* time data collected up to a time P can be observed to increase, *i.e.*, slightly beyond $t_{\min}$, is sufficient for the determination of all the kinetic constants. Further refinements in the estimated values can be obtained using data observed during subsequent dosing.

For a dose equivalent to C_p^0 administered at intervals of time equal to T, the variation of P with time in the $(n + 1)$ dosing interval can be obtained by successively solving Eqs. 2 and 3 to obtain Eq. 13:

$$P_{n+1}(T) = P_n(T)e^{-K_d\phi} - \frac{mK_e}{K_d^2}(1 - e^{-K_d\phi} - K_d\phi) - \frac{m}{K_d}(1 - e^{-K_d\phi}) \ln \left(\frac{C_p^0}{C_{p,\max}} S_e^{(n+1)} \right) \qquad \text{(Eq. 13)}$$

where:

$$\phi = t - nT \quad \text{(Eq. 14)}$$

$$P_n(T) = 100e^{-K_d nT} - \frac{mK_e}{K_d^2}(1 - e^{-K_d T} - K_d T)S_d^{(n)} - \frac{m}{K_d}(1 - e^{-K_e T})R_n(T) \quad \text{(Eq. 15)}$$

$$R_n(T) = \ln\left[\left(\frac{C_p^0}{C_{p,\max}}\right)^{S_d^{(n)}} S_e^{(n)} (S_e^{(n-1)})^{e^{-K_d T}} (S_e^{(n-2)})^{e^{-K_d 2T}} \cdots \times (S_e^{(1)})^{e^{-K_d(n-1)T}}\right] \quad \text{(Eq. 16)}$$

and:

$$S_e^{(i)} = \sum_{j=0}^{i-1} e^{-K_e jT} \quad \text{(Eq. 17)}$$

$$S_d^{(i)} = \sum_{j=0}^{i-1} e^{-K_d jT} \quad \text{(Eq. 18)}$$

Since, $S_e^{(1)}$ is unity, the last factor in the product $R_n(T)$ is given by Eq. 19:

$$S_e^{(1)e^{-K_d(n-1)T}} = 1 \quad \text{(Eq. 19)}$$

With some slight modification, the procedure described to obtain values for the kinetic parameters may also be used with Eq. 13 to utilize data observed during any dosing interval. Such analyses can be performed to increase the accuracy of the estimates of the parameters obtained from the first dosing interval or to obtain values for the parameters after dosing has been initiated.

The asymptotic form of Eq. 13, *i.e.*, for a large (theoretically infinite) number of doses, becomes relatively simple; it is shown as Eq. 20:

$$P_\infty = P_\infty(T)e^{-K_d t} - \frac{mK_e}{K_d^2}(1 - e^{-K_d t} - K_d t) - \frac{m}{K_d}(1 - e^{-K_d t}) \ln\left(\frac{C_p^0}{C_{p,\max}} S_e\right) \quad \text{(Eq. 20)}$$

where:

$$P_\infty(T) = \frac{-mK_e}{K_d^2}(1 - e^{-K_d T} - K_d T)S_d - \frac{m}{K_d}(1 - e^{-K_d T})S_d \ln\left(\frac{C_p^0}{C_{p,\max}} S_e\right) \quad \text{(Eq. 21)}$$

and:

$$S_e = \sum_{j=0}^{\infty} e^{-K_e jT} \quad \text{(Eq. 22)}$$

$$S_d = \sum_{j=0}^{\infty} e^{-K_d jT} \quad \text{(Eq. 23)}$$

Our computations reveal that for K_eT or K_dT values greater than 2, only very few terms are required in the summations, given by Eqs. 22 and 23, to approach their limiting values accurately.

A seemingly practical limitation in the application of the present approach to the characterization of the kinetics of hypoprothrombinemically responding systems is the inaccuracy that may be expected in the values of the parameters obtained from the use of graphically or numerically estimated values of first and second derivatives. The error in the parameter values may be diminished considerably, however, if instead of accepting the parameter values obtained directly from plots and computations involving the first and second derivatives (as provided by Eqs. 7 and 8) as final, these values are treated as merely initial estimates to be iteratively improved. The improvement can be accomplished through successive comparisons between experimentally determined and theoretical values of P—computed using either Eq. 6 or 13 as may be appropriate to a given set of data—as the parameters are systematically varied to converge iteratively with any desired degree of accuracy to provide values corresponding to a minimum in the sums of squares of the differences. Such an "iterative systematized guessing" approach was described previously (8, 9) and was successfully applied to achieve a similar "clean-up" of parameters arising in enzyme kinetic expressions (10), multiexponential fitting to drug level *versus* time data (9, 10), and the fitting of equations to describe dose–effect relationships (11–13).

When the kinetic parameters describing the pharmacological response behavior of a specific patient have been determined, these relations may be further applied to the computation of a dosage regimen appropriate for achieving specifically desired reductions in prothrombin complex activity or to the prediction of the magnitude of future therapeutic and/or toxic responses to a given dosage regimen.

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