Comparative Pharmacokinetics of Coumarin Anticoagulants XXXVI: Predicted Steady-State Patterns of Prothrombin Complex Activity Produced by Equieffective Doses of (*R*)-(+)- and (*S*)-(−)-Warfarin in Humans

Keyphrases □ Warfarin—(*R*)-(+)- and (*S*)-(−)-enantiomers, steady-state anticoagulant activity compared □ Coumarin anticoagulants—warfarin, (*R*)-(+)- and (*S*)-(−)-enantiomers, steady-state anticoagulant activity compared □ Pharmacokinetics—(*R*)-(+)- and (*S*)-(−)-warfarin, steady-state anticoagulant activity compared □ Anticoagulants—(*R*)-(+)- and (*S*)-(−)-warfarin, activity at steady state compared

To the Editor:

The biological half-life of (*S*)-(−)-warfarin is considerably shorter than that of (*R*)-(+)-warfarin in humans (1). However, the slope of the regression line relating anticoagulant effect and log plasma concentration for (*R*)-(+)-warfarin is considerably steeper than that for (*S*)-(−)-warfarin (2). It is of interest to compare the maximum and minimum anticoagulant activity during a dosing interval at the steady state produced by equieffective doses of the two enantiomers.

To assure adequate anticoagulation and to facilitate clinical monitoring of prothrombin complex activity, it is desirable to minimize the fluctuation of prothrombin complex activity during a dosing interval. Thus, if all else is equal, the enantiomer producing the least fluctuation of prothrombin complex activity during a dosing interval may be preferred therapeutically. Using average pharmacokinetic and pharmacodynamic parameters obtained in a study of 10 healthy men who received single doses of (*R*)-(+)- and (*S*)-(−)-warfarin on separate occasions (1, 2), we calculated the steady-state time course of prothrombin complex activity for each enantiomer during the usual dosing interval of 24 hr.

The calculations were performed in the following manner. The time course of plasma concentrations, C_t, for a one-compartment type drug administered in equal doses, D, at constant intervals, τ, in a manner resulting in essentially instantaneous absorption is:

$$C_t = \frac{D}{V}\left[\frac{1 - e^{-nk\tau}}{1 - e^{-k\tau}}\right]e^{-kt} \qquad \text{(Eq. 1)}$$

where V is the apparent volume of distribution, n is the number of doses administered, t is the time elapsed since dose n was administered, and k is the apparent first-order elimination rate constant (3). The right side of Eq. 1 was substituted for C_p in Eq. 1A of Nagashima *et al.* (4). When solved in the manner described by these investigators but with P^0 defined as the prothrombin complex activity (PCA) at the beginning of each dosing interval (so that P^0 changes with successive doses until a steady state is reached), the following relationship is obtained:

$$\text{PCA} = P^0 e^{-k_d t} + [1 - e^{-k_d t}] \times \left[\frac{R^0_{syn}}{k_d} - W \log \frac{C^0}{C_{p\,min}} - \frac{WZ}{k_d}\right] + WZt \qquad \text{(Eq. 2)}$$

where k_d is the apparent first-order degradation rate constant of prothrombin complex activity, C^0 is the drug concentration at $t = 0$ (calculated from Eq. 1), $Z = k/2.303$, and $W = m/k_d$. The parameters R^0_{syn} and R_{syn} are the synthesis rates of prothrombin complex activity before and during warfarin administration, respectively; m is the slope of a plot of R_{syn} *versus* the logarithm of the plasma warfarin concentration; and $C_{p\,min}$ is the intercept at R^0_{syn} of the extrapolated regression line of a plot of R_{syn} *versus* log plasma warfarin concentration (4).

The following parameter values were used in the calculations of prothrombin complex activity for (*R*)-(+)- and (*S*)-(−)-warfarin (listed in that order): k, 0.0129 and 0.0221 hr^{-1}; V, 99.2 and 95.4 ml/kg; m, −140 and −89%/day; and $C_{p\,min}$, 1.70 and 0.194 μg/ml. The k_d was 1.31 day^{-1}, P^0 before the first dose was 100% of normal, and τ was 24 hr. By successive trial calculations, a daily dose of (*R*)-(+)-warfarin suitable to produce a therapeutic range of prothrombin complex activity (≃30–35% of normal) was found to be 0.225 mg/kg; that of (*S*)-(−)-warfarin was 0.100 mg/kg. The calculations were carried out with a digital computer for $n = 24$.

The results of the simulations are shown in Fig. 1. The prothrombin complex activity *versus* time patterns for the two enantiomers were practically identical. In terms of clotting time, the difference between the maximum and minimum prothrombin complex activities is less than 1 sec. Thus, the greater fluctuation of (*S*)-(−)-enantiomer concentrations in plasma (due to its shorter half-life) is compensated by its more shallow effect–log concentration relationship. It appears, therefore, that there is no significant difference between the two enantiomers with respect to the constancy of prothrombin complex activity during a dosing interval. However, (*R*)-(+)-warfarin may be less subject to interactions with other drugs and may be the preferred form for that reason (5).

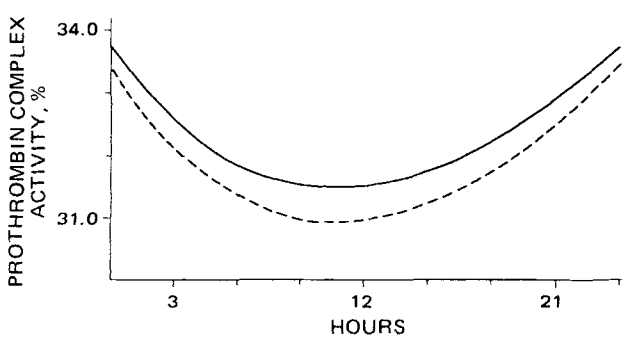

Figure 1—*Predicted time course of prothrombin complex activity in humans during a 24-hr dosing interval at the steady state during administration of essentially equieffective doses of* (R)-(+)-*warfarin* (——) *and* (S)-(−)-*warfarin* (- - - -).

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BOOKS

REVIEWS

Special Topics in Heterocyclic Chemistry. Vol. 30 of The Chemistry of Heterocyclic Compounds. Edited by ARNOLD WEISSBERGER and EDWARD C. TAYLOR. Wiley, 605 Third Ave., New York, NY 10016, 1977. 601 pp. 15 × 24 cm. Price $57.50.

Although this book is the 30th volume of a 25-year series of monographs on heterocyclic compounds, it is the first to contain treatments of various topics not necessarily related to each other or to a specific ring system. This volume, therefore, represents the editors' desire to discuss limited topics not requiring separate monographs.

The first four chapters share in common discussions of various bridgehead nitrogen heterocycles. Chapter I, 5,5-Systems with a Bridgehead Nitrogen Atom, by John P. Paolini, covers these conjugated 10π-electron heterocycles and their polycyclic derivatives but excludes cyclazines. Chapter II, Indolizine and Aza Derivatives with Additional Nitrogen in the 5-Membered Ring, by H. L. Blewitt, discusses indolizine and 1-, 2-, and 3-azaindolizines; the third chapter by Georges Maury covers azaindolizine systems having more than one nitrogen atom in the six-membered ring. Chapter III also includes azaindolizines containing diazines, triazines, and tetrazines together with pyrrolo-, imidazo-, *s*-triazolo-, and *v*-triazolo ring systems. Chapter IV, The Chemistry of Cyclazines, by Alfred Taurins,includes cycl[3.2.2]azines, cycl[3.3.2]azines, cycl[3.3.3]azines, 1-, 5-, 6-azacycl[3.2.2]azines, 1,4-diazacycl[3.2.2]azines, 8-azacycl[2.2.2]azines, and the 1,3,6-triaza-, 1,3,6,7-tetraza-, and 1,3,4,7-tetrazacycl[3.3.3]azines.

These four chapters are well coordinated, each covering synthetic methods, chemical properties, and physical properties including spectral properties and quantum chemical calculations. References following each chapter average 300 citations for the first three chapters. Chapters II and III include short sections relating to biological properties and uses. Very liberal usage of structural formulas in all but Chapter III makes it easy for the reader to follow the synthetic approaches to these systems.

Chapter V, Dithiole and Dithiolium Systems, by R. D. Hamilton and E. Campaigne, includes interesting discussions of the chemical reactivity of 1,2- and 1,3-dithiolium salts, illustrating their potential synthetic utility. Coverage of dithioles such as the thiothiophthene "no-bond" resonance system, dithiafulvalenes, and mesoionic systems does not proceed beyond the 1972 literature.

In a more up-to-date fashion (including references to the 1976 literature), heteropentalenes are reviewed in Chapter VI by Kevin T. Potts. Of the many possible heteropentalenes, this chapter is devoted to those heteropentalenes with ylidic characteristics, being 10π-electron systems representable by only charge-separated structures (dicoordinate, tetravalent sulfur-containing structures are included). The synthesis, physical properties, and chemical characteristics of these heteropentalenes containing heteroatoms at bridgehead or nonbridgehead positions and in one or both rings are presented in a clear and concise manner.

Chapter VII, Borazaromatic Compounds, by Albert J. Fritsch, treats heterocycles derived from benzenoid-type aromatic or heteroaromatic ring systems by replacement of a pair of carbon atoms by one atom each of boron and nitrogen. These include 2,1-borazarobenzene, 2,1-borazaronaphthalene, 10,9-borazaronaphthalene, 10,9-borazarophenanthrene, several five-membered borazaromatic compounds, and borazaromatic compounds containing another heteroatom in a six-membered ring. In addition to a section on spectral and theoretical considerations that undoubtedly provided initial stimulation in this area, an interesting section is devoted to the comparison of properties such as acidity, localization energies, and aromaticity of borazaromatic compounds.

The final and longest chapter (146 pages) is Syntheses and Properties of Cyanine and Related Dyes by David M. Sturmer. This review concentrates on dyes used as photographic spectral sensitizers and as desensitizers as opposed to those used in color imaging or antihalation and filtering. Sections on historical perspective and generic concepts serve to orientate the newcomer to this field rapidly. Of particular interest are the extended discussions of ground-state physical properties, electronic structure, substituent effects, and color shifts produced by isomerism and environment.

The inclusion of an appreciable amount of tabulated data throughout this volume enhances its value beyond its function of updating the reader in these specific areas.

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Narcotic Antagonists: The Search for Long-Acting Preparations, NIDA Research Monograph Series 4. Edited by ROBERT WILLETTE. National Institute on Drug Abuse, 11400 Rockville Pike, Rockville, MD 20852, 1977. 45 pp. 20 × 27 cm. Price $1.10.

Many pharmacologists and behavioral scientists believe that compulsive drug abuse is related to the reinforcing or satisfying properties of dependence-producing drugs. Since narcotic antagonists such as naloxone and naltrexone can entirely block the effects of ordinary doses of opioids, use of these drugs in the treatment of opiate addiction frequently has been advocated. However, in practice the narcotic antagonists have met with limited success, primarily because of their relatively short duration of action and the attendant problems of patient compliance.

The National Institute on Drug Abuse (NIDA), through its contractors, is attempting to develop a long-acting narcotic antagonist drug delivery system or a sustained-release preparation that can be used in the treatment of opiate addiction. This monograph contains abstracts and concise progress reports from seven NIDA supported projects. Six of the reports deal with the development of novel delivery systems. The approaches are quite varied and include the use of coated injectable microcapsules, sustained-release zinc and aluminum tannate complexes, and implantable polypeptide tubes filled with narcotic antagonist. One particularly interesting approach uses a dispersion of naltrexone in a bioerodable polymeric matrix to release drug at a predetermined, continuous, and substantially constant rate.

A seventh report describes the *in vivo* drug release characteristics and pharmacological activity of several delivery systems and also includes results of studies on the metabolic disposition and pharmacokinetics of naltrexone. Nearly all of the experimental data contained in the monograph are preliminary and preclinical. Only three reports list references.

Because of its very narrow scope, the monograph probably will be of major interest only to scientists presently engaged in research directly related to the development of long-acting pharmaceutical dosage forms. However, those persons who wish to keep abreast of current trends in the pharmacological control of compulsive opioid use also may find the monograph a source of useful, up-to-date information.

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