method. However, the same equation can be derived in a much simpler manner, which will be the subject of this communication.

The differential equation for describing the change of concentration of the substance with time during the zero-order input process is:

$$\frac{dC_p}{dt} = \frac{K_0}{V_d} - KC_p \qquad \text{(Eq. 2)}$$

where K is the apparent first-order elimination rate constant for the substance in the body. Equation 2 can be approximated to:

$$\frac{\Delta C_p}{\Delta t} = \frac{C_{p2} - C_{p1}}{t_2 - t_1} = \frac{K_0}{V_d} - KC_{p\,\text{mid}} \qquad \text{(Eq. 3)}$$

Since $C_{p\,\text{mid}}$ can be approximated to be equal to:

$$C_{p\,\text{mid}} = \frac{C_{p1} + C_{p2}}{2} \qquad \text{(Eq. 4)}$$

substitution of Eq. 4 into Eq. 3 results in the following relationship:

$$KV_d = \frac{2K_0}{C_{p1} + C_{p2}} + \frac{2V_d(C_{p1} - C_{p2})}{(C_{p1} + C_{p2})(t_2 - t_1)} \qquad \text{(Eq. 5)}$$

Since $TBC = KV_d$, Eq. 5 is the same as Eq. 1.

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Dose-Dependent Pharmacokinetics of 7-Chloro-1,3-dihydro-5-(2′-chlorophenyl)-2*H*-1,4-benzodiazepin-2-one in Dogs

Keyphrases ☐ 1,4-Benzodiazepine, substituted—chlorodesmethyldiazepam, pharmacokinetics in dogs ☐ Metabolites—chlorodesmethyldiazepam, pharmacokinetics in dogs ☐ Chlorodesmethyldiazepam—pharmacokinetics in dogs ☐ Pharmacokinetics—chlorodesmethyldiazepam in dogs

To the Editor:

7-Chloro-1,3-dihydro-5-(2′-chlorophenyl)-2*H*-1,4-benzodiazepin-2-one (chlorodesmethyldiazepam, I) is a major metabolite of 2-*o*-chlorobenzoyl-4-chloro-*N*-methyl-*N*′-glycylglycinanilide, a recently developed[1] minor tranquilizer. Compound I undergoes hydroxylation at the C-3 position and is converted to lorazepam (II) by liver microsomal enzymes of rats and mice (1).

When I was administered to dogs intravenously, its plasma level–time curves were dose dependent. No report has appeared concerning the dose-dependent metabolism and nonlinear pharmacokinetics of 1,4-benzodiazepines, in spite of many investigations on their metabolism and pharmacokinetics.

This communication describes a nonlinear pharmacokinetic model to explain the dose-dependent plasma concentration–time curve of I. Simulation values of parameters were derived from this model.

Two male dogs were injected with 0.5, 2.0, and 3.0 mg of I/kg iv. Plasma samples were collected from 10 min to 30 hr after injection. Compound I and free lorazepam were determined by GLC with an electron-capture detector[2]. Lorazepam glucuronide (III) in urine was determined after hydrolysis with glucuronidase–sulfatase. The plasma concentration–time curve following administration of 0.5 mg/kg declined linearly in two phases (distribution and elimination) on a semilogarithmic plot; the 2.0- and 3.0-mg/kg doses gave curves of convex shape after distribution had been completed, with a more pronounced curvature for the higher dose. However, the apparent plasma half-lives of I estimated from the terminal straight region of the curves were nearly equal for the three doses. The plasma concentration–time curves of I, as already mentioned, would exclude enterohepatic circulation as a main elimination pathway of I and/or a conjugate of I. In urine, the major metabolite was lorazepam glucuronide (35%), and only 0.05% of the unchanged drug (total of free and conjugated forms) was excreted over 54 hr. Other metabolites were not detected.

Ethyl alcohol (2) and phenytoin (3) show dose-dependent pharmacokinetics that fit a one-compartment model including the Michaelis–Menten equation.

The most simplified model for the plasma concentration–time curves of I is elaborated on the following assumptions: enterohepatic circulation of I and/or its glucuronide is negligible, and enzymes concerned with the metabolism of I have the same enzyme constants (V_m and K_m). Model equations employed for the plasma level–time curves of I are shown as Eqs. 1 and 2 but cannot be solved with the data of plasma levels only:

$$V_1\frac{dC_1}{dt} = V_2k_{21}C_2 - V_1\left(k_{12}C_1 + \frac{V_mC_1}{K_m + C_1}\right) \qquad \text{(Eq. 1)}$$

$$V_2\frac{dC_2}{dt} = V_1k_{12}C_1 - V_2k_{21}C_2 \qquad \text{(Eq. 2)}$$

Therefore, digital computer simulation was performed by the Runge–Kutta method using the kinetic parameters k_{12}, k_{21}, V_1, and V_2 estimated from the linear two-compartment open model at 0.5 mg/kg. The simulation curves produced a satisfactory fit for the 2.0- and 3.0-mg/kg data. The simulation values obtained were 0.58 and 1.30 μM/hr for V_m and 0.50 and 1.00 μM for K_m in Dogs 1 and 2, respectively. Ten- and one-tenthfold multiple transformations of the simulated V_m and K_m values gave curves significantly different from the experimental data.

These results support the kinetics in which the plasma decline of I obeys the two-compartment model, including

[1] Unpublished results.

[2] To be published.

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the Michaelis–Menten equation. Further investigations on the metabolism and extrarenal excretion of I should confirm the described model.

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BOOKS

REVIEWS

Drug Disposition During Development. Edited by PAOLO LUCIO MORSELLI. Spectrum, 170-20 Wexford Terrace, Jamaica, NY 11423. 1977. 490 pp. 15 × 25 cm. Price $40.00.

The editor of this multiauthored book is outstanding in the field of developmental pharmacology and has gained an international reputation of excellence.

The book is intended to provide investigators, clinical pharmacologists, pediatricians, general practitioners, and medical students with an understanding of the information available on the influence of age on drug disposition and effects from birth to adulthood.

It should be especially valuable to clinical pharmacists and certainly to those relating to children's therapy. There are a number of basic chapters, *e.g.*, pharmacokinetics, DME, and development of enzymes and organs as related to children.

The remaining chapters deal with various drug classes, all as related to the several age groups of childhood. The book accomplishes its purpose clearly and concisely and provides for further excursions into the literature by well-chosen references.

Those who are concerned with children's drug treatment need this book. It is clinically oriented and will be frequently consulted.

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New Drugs: Discovery and Development. (Drugs and the Pharmaceutical Sciences Series, Vol. 5). Edited by ALAN A. RUBIN. Dekker, 270 Madison Ave., New York, NY 10016. 1978. 328 pp. 15 × 23 cm. Price $35.00.

This fifth volume of the Drugs and the Pharmaceutical Sciences Series reviews pertinent background, methodology, present status, and future expectations of nine selected topics in modern drug research. It is unique in that it offers this information from the vantage point of the industrial researcher. All contributors to this volume conduct their research in pharmaceutical company settings where high screening capacity, cost effectiveness, and judicious manpower allocations play a critical role in the search for new drugs. This book discusses the fine balance between these scientific and economic considerations which is vital for successful industrial research.

The nine subjects covered in this volume were selected on the basis of their broad research appeal; they include four chapters on the central nervous system (major and minor tranquilizers, antidepressants, and analgesics), three chapters on the cardiovascular system (antianginals, antiarrhythmics, and antihypertensives), and one each on allergy and arthritis. The authors discuss their personal views concerning the strengths and weaknesses of current drug evaluation methodology, the profile of an ideal drug, and anticipated future developments in their respective areas of expertise.

With 896 references and comprehensive author and subject indexes, this book serves as a timely laboratory guide and desk reference for biologists and chemists involved in pharmaceutical research, whether it be in private industry or academia. It is of particular interest to pharmacologists responsible for evaluation and development of drugs affecting arthritis, allergies, the central nervous system, and the cardiovascular system.

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NOTICES

Affinity Chromatography. Journal of Chromatography Library, Vol. 12. By JAROSLAVA TURKOVA. Elsevier Scientific, 52 Vanderbilt Ave., New York, NY 10017. 1978. 405 pp. 18 × 24 cm. Price $69.75.

Fiches de Dosages des Medicaments dans les Millieux Biologiques. Edited by B. FLOUVAT. Expansion Scientifique, 15 Rue Saint-Benoit, 75278 Paris Cedex 06, France. 1978. 21 × 27 cm. Price 75 F.

IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man. World Health Organization, 49 Sheridan Ave., Albany, NY 12210. 18 × 24 cm.

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Vol. 15: Some Fumigants, the Herbicides, 2,4-D and 2,4,5-T, chlorinated Dibenzodioxins, and Miscellaneous Industrial Chemicals. 1977. 354 pp.