(6) G. Levy, C.-M. Lai, and A. Yacobi, *ibid.*, **67**, 229 (1978).
(7) A. Yacobi and G. Levy, *ibid.*, **66**, 567 (1977).
(8) H.-S. G. Chen and J. F. Gross, *J. Pharmacokinet. Biopharm.*, **7**, 117 (1979).
(9) M. Kekki, R. J. K. Julkunen, and B. Wahlström, *Naunym-Schmiedebergs Arch. Pharmacol.*, **297**, 61 (1977).

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Previous paper in this series: J. W. Crow, M. Gibaldi, and G. Levy, *J. Pharm. Sci.*, **68**, 1309 (1979).

COMMUNICATIONS

Pharmacokinetics of *cis*-Dichlorodiammine Platinum(II) in Rats Using an External Loop–Eigenfunction Expansion Technique

Keyphrases □ Pharmacokinetics—organometallic antineoplastic agents, external loop blood sampling techniques, eigenfunction expansion analysis, Fourier transform analysis □ External loop technique—blood collection, pharmacokinetics, eigenfunction expansion analysis □ Antineoplastic agents—organometallic, pharmacokinetics, external loop technique, eigenfunction expansion analysis

To the Editor:

An external loop technique for collecting many closely spaced blood concentration–time data points, early in an experiment when the concentration changes rapidly, was developed recently for compounds labeled with γ-emitting isotopes (1, 2). The large amount of accurate data collected at such frequent intervals allows the use of the more objective methods of Fourier transform or eigenfunction expansion analysis for the determination of pharmacokinetic parameters.

With conventional data collection methods, determination of the optimum number of exponentials necessary to describe adequately the time course of the drug is difficult. With a limited number of data points collected over a relatively short period (4–6 hr), a maximum of three exponentials has been suggested (3). For studies conducted over several days, it is possible to resolve more exponentials (4).

The external loop method permits continuous monitoring of radiopharmaceuticals and provides several advantages over traditional blood sampling techniques:

1. There is no sampling time error.
2. The number of samples is ~500 *versus* 40 since there is no blood volume loss to limit the sampling.
3. The sample volume does not change. Such a change affects both the compartment size and the loss of activity.
4. The continuous cumulative count of the analyzer gives an accurate average activity over the time interval.
5. The time interval may be varied or kept constant with a lower limit of less than a millisecond. This flexibility allows the collection of different data sets, thus enhancing numerical analysis by gaining more information at a crucial time.

The large amount of data collected permits the use of Fourier transform analysis to resolve the number of exponentials. Fourier transform analysis was used previously to analyze multicomponent exponential decay curves (5–8). By this method, it is possible to transform the raw data and obtain a plot of the transformed data *versus* the rate constants (λ). The major contributing rate constants can be determined as major peaks in this curve. Provencher (9) recently described a digital computer program for data analysis (9) that is described by a multiexponential equation using the Fourier transform method proposed by Gardner *et al.* (5, 6). Subsequently, an alternative method using an eigenfunction procedure was proposed (10).

cis-Dichlorodiammine platinum(II) (I) represents the first of a series of organometallic antineoplastic agents to be marketed. This compound is used clinically, particularly in the treatment of metastatic testicular carcinoma. Pharmacokinetic parameters for the platinum moiety from I were determined in the rat using traditional blood sampling techniques (4, 11) and an external loop method (2). As an initial step in further studies using I and related agents, we investigated the kinetics of I using an external loop and analyzed the data with an eigenfunction procedure[1].

Male Sprague–Dawley rats, 300–350 g, were prepared as previously described (1). Hexachloroplatinic acid containing platinum-195m[2] was used as the starting material

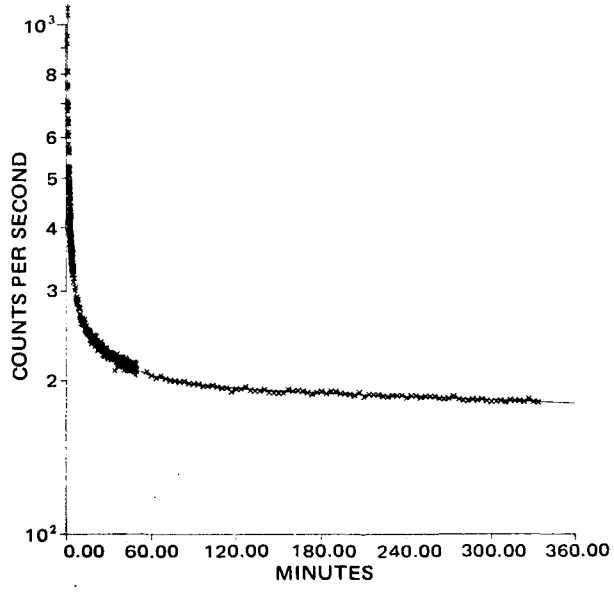

Figure 1—*Plot of counts per second* (×) versus *time measured in an external blood loop following intravenous administration of 1.1 mg of* cis*-dichlorodiammine platinum(II)/kg to Rat 1. The solid line was calculated using the equation that best fit the data.*

[1] A digitial computer program for performing the analysis was kindly provided by S. W. Provencher, Max-Planck-Institut fur Biophysikalische Chemie, D-3400 Gottingen-Nikolausberg, Federal Republic of Germany.
[2] Oak Ridge National Laboratory, Oak Ridge, Tenn.

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to prepare radiolabeled I using a modified literature method (12). Each rat received 1.1 mg of I/kg iv, corresponding to $\simeq 100$ μCi. Data were collected every 2 sec for the first 300 sec, every 20 sec for the next 3000 sec, and every 200 sec until the end of the study. Radioactivity measured in the loop was corrected for decay and background.

A typical plot showing the results obtained is shown in Fig. 1. The data were weighted inversely to the time interval of collection and analyzed by the program of Provencher[1]. The computer program automatically selected the best number of exponential terms required by the data according to an F test with a nonlinearity correction. The best-fit values for the rate constants were 7.90, 1.45, 2.96 $\times 10^{-1}$, 3.50 $\times 10^{-2}$, and 2.52 $\times 10^{-4}$ min^{-1} for Rat 1 and 4.18, 1.10, 2.69 $\times 10^{-1}$, 3.33 $\times 10^{-2}$, and 1.60 $\times 10^{-4}$ min^{-1} for Rat 2. The five-exponential equation that gave the best fit to the data for Rat 1 was used to calculate the solid line in Fig. 1. The fastest observed rate constant may be due to a mixing or rapid distribution within the animal; however, the remaining four exponentials are similar to the values obtained previously (2, 4).

(1) J. W. Triplett, D. W. A. Bourne, and R. B. Smith, *Int. J. Appl. Radiat. Isot.*, **29**, 189 (1978).

(2) W. Wolf and R. C. Manaka, *J. Clin. Hematol. Oncol.*, **7**, 79 (1977).

(3) R. F. Brown, F. R. Carson, L. Finkelstein, K. R. Godfrey, and R. P. Jones, *Med. Biol. Eng. Comput.*, **17**, 216 (1979).

(4) D. M. Taylor, *Biochimie*, **60**, 949 (1978).

(5) D. G. Gardner, J. C. Gardner, G. Laush, and W. W. Meinke, *J. Chem. Phys.*, **31**, 978 (1959).

(6) D. G. Gardner, *Ann. N.Y. Acad. Sci.*, **108**, 195 (1963).

(7) S. M. Pizer, A. B. Ashare, A. B. Callahan, and G. L. Brownell, in "Biomathematics," vol. I, "Concepts and Models of Biomathematics Simulation Technqiues and Methods," F. Heinmets, Ed., Dekker, New York, N.Y., 1969, p. 105.

(8) A. B. Callahan and S. M. Pizer, in "Natural Automata and Useful Simulations," H. Patter, Ed., Spartan, Washington, D.C., 1966, p. 149.

(9) S. W. Provencher, *Biophys. J.*, **16**, 27 (1976).

(10) S. W. Provencher, *J. Chem. Phys.*, **64**, 2772 (1976).

(11) C. L. Litterst, I. J. Torres, and A. M. Guarino, *J. Clin. Hematol. Oncol.*, **7**, 169 (1977).

(12) S. C. Dhara, *Indian J. Chem.*, **8**, 193 (1970).

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BOOKS

Terpenoids and Steroids, Vol. 8. Senior Reporter, J. R. HANSON. The Chemical Society, Burlington House, London W1V OBN, England. 1978. 301 pp. 15 × 22 cm. Price $50.00. (Available from Special Issues Sales, American Chemical Society, 1155 16th St., N.W., Washington, DC 20036.)

This book is the eighth volume on terpenoids and steroids in a valuable series initiated 8 years ago. The aim of each series of Specialist Periodical Reports is to provide a systematic, comprehensive, and critical review of progress in the major areas of chemical research. The various series, which now total 36, are published annually or biennially on such topics as Environmental Chemistry; Biosynthesis; Foreign Compound Metabolism in Mammals; The Alkaloids; Carbohydrate Chemistry; Amino-acids, Peptides, and Proteins; and Photochemistry.

This volume does not contain a subject index, but it is organized in a systematic manner which facilitates finding any desired information. The five pages in the Table of Contents outline this volume in detail. The chapters are divided into many sections, which are identified in bold type in the text as well as in the Table of Contents. These sections are divided into subsections. Chapter titles are found at the top of every other page of the text. The author index includes 3300 names and is helpful to anyone following the research of a given individual.

This review is illustrated with drawings of 1700 chemical structures. It is documented with 1650 references, most of which are listed at the bottom of the page where first used in a given chapter.

Part I covers the terpenoids and is divided into chapters that include Monoterpenoids, Sesquiterpenoids, Diterpenoids, Triterpenoids, and Carotenoids and Polyterpenoids. Part II, which covers steroids, is divided into two chapters entitled Physical Properties, and Steroid Reactions and Partial Syntheses. No compilation of references to review articles on subjects related to terpenoids or steroids is included in this volume as in many of the previous volumes.

The chapter on Steroid Reactions and Partial Syntheses is long and is divided into two sections. The first section is divided into subsections based on more common functional groups, a subsection on compounds of nitrogen, sulfur, and selenium, and subsections on such important topics as molecular rearrangements, functionalization of nonactivated positions, and photochemical reactions. The section on partial syntheses is divided into the following subsections: cholestane derivatives and analogs, vitamin D and its metabolites, pregnanes, androstones, cardenolides, secosteroids and cydosteroids, heterocyclic steroids, microbiological oxidations and reductions, and miscellaneous syntheses.

The editor and six reporters who prepared this volume are to be commended for maintaining the high standards set by the previous volumes in this series. Everyone interested in the chemistry of terpenoids and/or steroids should have access to this volume and others in the series. Many terpene and steroid chemists will want copies on their desk. This series is a great timesaver and a source of many ideas. I highly recommend it.

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