$$C_{ss}^{min} = \frac{p_1 e^{-p_2(x+4)}}{1 + e^{p_3 - p_4(x+4)}} \qquad \text{(Eq. 14)}$$

$$\bar{C}_{ss} = \frac{1}{4}\int_x^{x+4} \frac{p_1 e^{-p_2 t}}{1 + e^{p_3 - p_4 t}}\, dt \qquad \text{(Eq. 15)}$$

The integral in Eq. 15 was evaluated numerically by a commonly used integration algorithm (4).

Special caution must be taken in applying a loading dose of a nonlinear drug. It may not be desirable to use a loading dose for a drug showing a narrow therapeutic index. However, in certain clinical situations it may be necessary to quickly establish high therapeutic levels by a loading dose. For example, the treatment of an epileptic emergency may call for an intravenous loading dose of phenytoin (5). The loading dose required for the method only needs to be slightly larger than a normal loading dose.[1] It should, therefore, not add much additional risk to the administration of such a loading dose. The method may also be used in dosing adjustments requiring lower steady-state drug levels, in which case the drug level data needed to make the predictions may be obtained from the later part of the dosing period.

[1] However, if the function $g(\ )$ is well chosen, it can be used to extrapolate to required levels and a loading dose may not be required.

(1) ZBRENT, IMSL, Houston, Texas.

(2) G. Dahlquist and A. Björk, "Numerical Methods," Prentice-Hall, Inglewood Cliffs, N.J., 1974, Chap. 6.

(3) P. Veng-Pedersen, *J. Pharmacokinet. Biopharm.*, **5**, 513 (1977).

(4) C. deBoor, in "Mathematical Software," J. Rice, Ed., Academic, New York, N.Y., 1971, Chap. 7.

(5) M. E. Winter, "Basic Clinical Pharmacokinetics," Applied Therapeutics Inc., San Francisco, Calif., 1980, p. 183.

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BOOKS

Progress in Medicinal Chemistry, Vol. 19. Edited by G. P. ELLIS and G. B. WEST. Elsevier Biomedical Press BV, Amsterdam, The Netherlands. 1982. 345 pp. 14 × 21 cm. Price $93.50 (Dfl. 220).

Contained in this volume are six reviews of independent topics covering a variety of subjects. Chapter I, "Immunopharmacology of Gold," by A. J. Lewis and D. T. Walz denotes the pathology of rheumatoid arthritis, the historical use of gold for therapeutic purposes, pharmacokinetics of gold compounds, and gold–protein interaction with tissue sulfhydryl groups, hydrolytic enzyme, prostaglandin synthetase complement, and collagen. The response systems as well as their current clinical uses in rheumatoid arthritis, pemphigus, asthma, and cancer are described.

Chapter II, "Calcium and Histamine Secretion from Mast Cells," by F. L. Pearce deals with the role of calcium in histamine release, membrane ionophones, phospholipid vesicles and permeability, and calcium pools inside and outside the cell. The activation of vasoamine release by the mast cell *via* the translocation of calcium was related to membrane phosphatidylinositol metabolism, phospholipid methylation, and cAMP levels. Known inhibitors of these processes were evaluated.

Chapter III, "Biological and Pharmacological Properties of Phospholipids," by A. Bruni and P. Palatini is a discussion of the phospholipid bilayer model including flexibility, stability, asymmetry, head groups, and fusion of the components. Phospholipid–protein interrelations, including lipid-binding proteins, mode of association, specificity of the interreaction, mutual influence of components in the membrane, and structural models are presented. The pharmacological aspects of liposomes or bilayer envelopes including pharmacokinetics; interaction with cells; delivery of drugs, genetic material, or immune components; and lipid chemical mediators were presented by the authors.

Chapter IV, "Cyclophosphamide Analogues," by G. Zon includes a cursory historical review of cyclophosphamide as an antineoplastic agent including novel chemical substitutions, related conformational effects, prodrug models, structure–activity relationships of active metabolites, and miscellaneous analogues.

Chapter V, "Chartruesin, a Glycosidic Antitumor Antibiotic from *Streptomyces*," by J. A. Beisler covers the natural, microbial, and biochemical sources and structure determination of chartruesin. Partial and total synthetic routes of aglycones are reviewed. The antitumor activity, mode of action, and toxicity of chartruesin are briefly eluded to in the discussion.

Chapter VI, "Recent Progress in the Medicinal Chemistry of 2,4-Diaminopyrimidines," by B. Roth and C. C. Cheng covers the classical aspects of antimetabolites of folic acid and descriptions of dihydrofolate reductase enzymes from bacteria and vertebrate sources. Pharmacological action was discussed in three areas: (*a*) antibacterial action of diaminopyrimidines of the 2,4-diamino-5-(substituted benzyl) pyrimidines, 6-substituted 2,4-diamino-5-benzyl pyrimidines, isosteres of the benzylpyrimidines, dihydro-*sym*-triazines, and bicyclic analogues of diamino-pyrimidines; (*b*) antimalarial dihydrofolate reductase inhibitors—pyrimethamine and cycloguanil, monocyclic 2,4-diamino-pyrimidines and isosteres, dihydro-*sym*-triazines, and quinazolines; (*c*) anticancer—dihydrofolate reductase inhibitions by methotrexate, modifications of the glutamic acid, benzene ring, bridge atoms between the rings, and pteridine portions. Miscellaneous and nonclassical dihydrofolate reductase inhibitors are included in the chapter.

Whereas all six of these topics are relevant to medicinal chemistry, this reviewer found the text somewhat disappointing from two aspects: (*a*) much of the material was redundant with basic conceptual ideas presented on numerous occasions in the literature; (*b*) the topics selected were not those that would be at the forefront of current research today. However, the chapters are well referenced with a number of figures, tables, and diagrams, and the text is organized and clearly written for understanding by the reader. The major use of the text as a reference book would be for graduate students and individuals not versed in these areas of research. The current status of each of the six topics is accurately assessed by the authors, and the text is an excellent overview of both chemical and biological ideas regarding the topics, which is important in medicinal chemistry because of the diversity of the field.

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