PERSPECTIVES IN PHARMACOKINETICS

Linear and Nonlinear System Approaches in Pharmacokinetics: How Much Do They Have to Offer? II. The Response Mapping Operator (RMO) Approach

Peter Veng-Pedersen

Commentaries by Ronald A. Siegel, Harold Boxenbaum, and Carl M. Metzler

The description of the relationship between different responses measured simultaneously in the same subject is commonly described in terms of specific pharmacokinetic models such as linear compartmental models. An alternative system approach involving response mapping operators (RMOs) is presented. The theoretical and mathematical basis of the RMO approach are derived. The assumptions, limitations, and practical significance of the RMO approach are discussed. The derivation of the RMO is illustrated with several examples. An algorithm and computer program for implementing the RMO in a routine manner is presented. The usage of the computer programs RMO and MAP presented are demonstrated using the pharmacokinetics of trimazosin and cefamandole in humans as examples. The RMO approach offers a new and powerful tool in pharmacokinetic analysis, which allows the investigator to approach certain problems in an objective, rational way without getting involved in specific pharmacokinetic modeling.

KEY WORDS: pharmacokinetic modeling, linear system approach; pharmacokinetic response relationships; response mapping; response mapping operators; pharmacokinetic algorithm; pharmacokinetic computer programs.

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2College of Pharmacy, University of Iowa, Iowa City, Iowa 52242.
3Ronald A. Siegel, Department of Pharmacy, School of Pharmacy, University of California, San Francisco, California 94143-0446.
4Harold Boxenbaum, Merrell Dow Research Institute, 2110 E. Galbraith Road, P.O. Box 156300, Cincinnati, Ohio 45215-6300.
5Carl M. Metzler, The Upjohn Company, Kalamazoo, Michigan 49001.
INTRODUCTION

This work deals with pharmacokinetic systems where two or more simultaneous responses are being analyzed. Typically the responses may be concentration vs. time responses of drug and/or metabolites in different tissues, e.g., blood, cerebrospinal fluid, brain tissue, adipose tissue, tumor tissue. However other types of responses may also be involved such as urinary excretion rate; rate of metabolism; rate of transport of drug into a tissue (e.g., tumor drug uptake); amount of drug remaining in the body, a tissue, or an organ.

Attempts are often made to describe such systems by the use of specific pharmacokinetic models. This leaves the investigator in the quite subjective realm of modeling. The task of identifying a model among the many possibilities within the many classes of models (compartmental, recirculation, physiological, stochastic, etc.) appears difficult and quite involved for theoretical, mathematical, and computational reasons. All too often the end result of such modeling endeavors seems to be of more theoretical than practical significance.

This work presents an alternative, rational approach. The approach avoids the difficult task of modeling the “topology” of the pharmacokinetic system. In the proposed approach it is not necessary to model specifically the individual kinetic processes which are responsible for the responses considered. In spite of this lack of specific modeling the approach provides an exact mathematical relationship between the responses of interest through the use of response mapping operators (RMOs). The purposes of this communication are (i) to present the theory behind RMOs, (ii) to present an algorithm and computer program that enables RMOs to be determined and applied simply as a routine procedure; (iii) to give some simple examples to illustrate how RMOs are derived mathematically; (iv) to demonstrate the automatic computer generation of RMOs, and show how RMOs are applied using the pharmacokinetics of trimazosin and cefamandole as examples; and (v) to discuss the limitations and assumptions of the RMO approach and discuss its practical significance.

THEORY

Let $\mathcal{R}_1(t)$ and $\mathcal{R}_2(t)$ be two simultaneous pharmacokinetic responses being investigated. Let it be assumed that $\mathcal{R}_1(t)$ and $\mathcal{R}_2(t)$ depend on a third function $f(t)$ in a linear way defined in general terms by the following linear

$6$Although $c(t)$ is the common terminology for concentration response the term should be viewed in a more general sense simply as a response of some kind. See Glossary for definition of terms.