Estimation of Population Characteristics of Pharmacokinetic Parameters from Routine Clinical Data

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A general data analysis technique estimates average population values of pharmacokinetic parameters and their interindividual variability from clinical pharmacokinetic data gathered during the routine care of patients. Several drug concentration values from each individual, along with dosage information and the values of other routinely assessed variables suffice for purposes of analysis. The Maximum Likelihood principle estimates underlying population values without the necessity for the intermediate estimation of individual parameter values. The approach is quite general, permitting the use of nonlinear statistical models with both fixed and random effects. Complex expressions involving physiological variables can be used to define the pharmacokinetic parameters. Thus, the relationship of physiological factors to parameter values can be assessed. The generality and appropriateness of the analysis technique are demonstrated by analysis of a set of data derived from 141 patients receiving the drug digoxin.

KEY WORDS: statistics; parameter estimation; maximum likelihood; population parameters.

INTRODUCTION

There is considerable current interest in determining the population characteristics of pharmacokinetic parameters describing drug absorption and disposition, and a great deal of experimental work has been devoted to this end. Population characteristics include (1) the mean values of parameters, (2) their quantitative relationship to individual physiology (e.g., body size, function of liver, kidney, or heart, and so forth), and (3) their variability.
across populations of patients. All three aspects of the distribution of pharmacokinetic parameters are of interest because they are required for the optimal design of dosage regimens for individual patients, and because they provide insight into the mechanisms by which drugs are absorbed, distributed, and eliminated.

A major impediment to obtaining such information is the difficulty and cost of measuring enough plasma drug concentrations to permit estimation of individual pharmacokinetics in enough individuals to represent a patient population. The apparent belief has been that only data of this nature can provide accurate population estimates. If, however, pharmacokinetic data consisting of only a few concentration measurements from each individual patient could be used to derive population value estimates, the estimates could be obtained inexpensively and would be especially meaningful—inexpensively, because such data are essentially costless, as they are already being generated increasingly in the routine care of patients for purposes of monitoring drug therapy, and especially meaningful, because population value estimates derived from such data would reflect the populations actually receiving the drugs, rather than normal volunteers.

A number of years ago, we proposed an approach to the analysis of pharmacokinetic data which permitted derivation of population values from routine patient data (1). We applied the analysis to some data for digoxin and were subsequently able to show that the population estimates obtained by our analysis were valuable for one of the uses mentioned above: guiding the selection of individual patients' dosage (2,3). Since that time, we have, we believe, confirmed the validity of our approach. We believe that it is now timely to stress the advantages of our data analysis method. This article will therefore describe the general approach in the context of the application to digoxin.

To do so, this article proceeds as follows: First, the problem is considered in terms of the types of questions we wish to answer about the population parameters. Second, the analysis of routine patient data is contrasted with a more traditional approach, and the advantages and disadvantages of each are explored. Third, a very simple example of a pharmacokinetic model is presented for illustrative purposes. In the context of this model, the mathematical and statistical devices required to estimate its population parameters using routine patient data are developed and discussed. Fourth, some results of the application of the methodology to data concerning digoxin are presented. The model used to analyze the actual data is a great deal more complex than the simple illustrative one discussed previously. It is therefore presented later, in the Appendix, so that we may focus, in this section, on the results themselves. Fifth, and finally, we summarize and further discuss the applicability of our approach.