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Population pharmacokinetics: theory and practice

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Recently, there has been a lot of activity in the area of population pharmacokinetics, stimulated by a number of enthusiasts and also by attitudes within the U.S. Food and Drug Administration (FDA). Population pharmacokinetics can be defined as the study of the variability in plasma drug concentrations between individuals when standard dosage regimens are administered. It is of interest both to measure this variability within the population and to account for it in terms of patient variables, such as age, sex, weight or disease state. Scientists who have been working in the area of pharmacokinetics for a number of years may well ask whether the definition given above is any different from what they have always understood to be the main purpose of pharmacokinetics. (An indiscriminate search of a data base such as Index Medicus using the keywords population and pharmacokinetics will quickly confirm this). For twenty or thirty years the pharmacokinetics of a vast number of drugs (and indeed xenobiotics in general) in a variety of different patient populations have been studied with a view towards understanding the factors affecting the absorption, distribution and elimination of these drugs and to aid in the design of dosage regimens. So who are the new breed of population pharmacokineticists?

The current interest in population pharmacokinetics stems from the concern that the pharmacokinetics of new drugs are not studied in relevant populations, that is patients likely to receive the drug, at an early enough stage in the drug development program. In particular the FDA (Temple, 1983, 1985) and others (Abernathy & Azarnoff, 1990) are concerned that the pharmacokinetics of a new drug should be studied in elderly populations 'so that physicians will have sufficient information to use drugs properly in their older patients' (F.D.A., 1989). The obvious time to collect pharmacokinetic information on the target population is during large-scale clinical trials carried out during Phase III of the drug development program. However, because of logistic and ethical reasons, it is improbable that intensive experimentation can be carried out on each and every patient. At best one could hope for one or two blood samples per patient. Therefore traditional pharmacokinetic analysis, which involves the determination of an individual's pharmacokinetic parameters, is not feasible. Instead data analysis techniques that focus on the central tendency of the pharmacokinetic information and are capable of utilizing very sparse data have to be employed. Population pharmacokinetics has come to mean the design, execution and analysis of pharmacokinetic studies involving sparse data, although the data analysis techniques can be applied to data obtained from conventional pharmacokinetic studies. The label population pharmacokinetics is perhaps unfortunate, but it does convey the sentiment that interest is focused on the population rather than the individual.

To date most population pharmacokinetic studies have been carried out within a clinical setting (Whiting *et al.*, 1986). One major aim of these studies has been to establish guidelines for the adjustment of dosage regimens to be used together with Therapeutic Drug Monitoring and a Bayesian feedback algorithm (Sheiner & Beal, 1982; Vozeh & Steiner, 1987). The data collection in these studies has in general been well controlled and compliance has not been a major issue. There is an increased interest in the application of population approaches to the drug development programme (Grasela *et al.*, 1986; Graves *et al.*, 1989). However it is early days yet, and it will be some time before interested parties within the pharmaceutical industry have evaluated the approach. The application of population techniques in the fields of cancer chemotherapy (Gitterman *et al.*, 1990; Launay *et al.*, 1989) and neonatal therapy (Driscoll *et al.*, 1989; Kelman *et al.*, 1984; Moore *et al.*, 1989), which for different reasons generate sparse data, is particularly exciting and we should see a growth of applications in these areas.

It was pointed out above that within the modern meaning of population pharmacokinetics there is a need to analyze sparse data sets, and that this requires specialized data analysis techniques. From a statistical point of view the data are related to a nonlinear mixed effects model involving repeated measures, and Beal & Sheiner (1982) have been instrumental in bringing the methods for analyzing such data to the attention of interested scientists. Unfortunately the computer package NONMEM, developed by Beal & Sheiner (1982), has become synonymous with population pharmacokinetics. Population pharmacokinetics is a discipline, whereas NONMEM is a software package capable of analyzing data arising from population pharmacokinetic studies and the two are (almost) independent. Having said that, the analysis of sparse data requires sophisticated methodology and its complexity has led a number of people to shy away from the discipline. The way forward is probably through co-operation between pharmacokineticists and individuals who have the necessary skills in analyzing sparse data.

NONMEM is not the only method available for the analysis of population pharmacokinetic data, but it is the most widely used package. Other approaches include a nonparametric maximum likelihood method (Mallet, 1986); Bayesian methods (Racine-Poon & Smith, 1990); and variants of the nonlinear mixed effect model (Amisaki & Tatsuhara, 1988; Lindstrom & Bates, 1990). Steimer *et al.* (1984) review some of the earlier methods. There

is some debate about the pros and cons of the various methods, including such issues as software availability, reliability and robustness. However, these arguments tend to detract from the philosophy of the population approach. Essentially any reasonable method will suffice—the data rather than the data analysis present the real problem.

The implementation of a population approach within drug development programs is the subject of much recent debate (Colburn, 1989). It has been suggested that a 'population screen' be employed in which blood samples are taken from a wide range of individuals so that, essentially, the concentration-time profile is covered within the population (Sheiner & Benet, 1985). The advantages of such an approach are that data are collected in the target population, an assessment of the variability within the population is obtained and, hopefully, the factors that control that variability may be discovered. Although desirability of these goals is indisputable, much concern has been expressed about the logistics of implementing a population approach during Phase III of the drug development program. A comment frequently made is 'garbage in, garbage out'. Of couse this criticism can made of any poorly designed or executed study, not just population studies. However there are particular problems associated with Phase III studies in that they are generally multicentre and in many cases conducted in outpatients. Compliance and accurate timing of both dosing and sampling are clearly critical issues. At present there are virtually no guidelines on experimental design, either in terms of sample timing or subject numbers, particularly within subgroups. Similarly, we have no idea of the power of the approach to detect important intersubject differences and overall there is no hard data on the cost-to-benefit ratio. If the current level of interest is maintained these important issues will be addressed and the future looks exciting. At present we are still on the learning curve.

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