Variability in Human Drug Response
G.T. Tucker, Editor


# Population Modelling

Leon Aarons

School of Pharmacy and Pharmaceutical Sciences, University of Manchester, Manchester, U.K.

## ABSTRACT

Frequently dosing recommendations that emerge from a clinical drug development program are found inappropriate and when individual dose adjustment is needed, the recommendations provided may not be informative enough to allow the adjustment to be undertaken in an optimal manner. Frequently, and particularly in the later stages of drug development, only relatively sparse observational concentration and effect data are available. Recently developed statistical methods offer the possibility of gaining integrated information on pharmacokinetics and response from such data, obtained directly in patients who are being treated with the drug under development. The methods allow the incorporation of data from patient groups which are often excluded from classically designed clinical trials and also the analysis of a variety of unbalanced designs that frequently arise in the evaluation of dose or concentration- efficacy and -safety profiles, which do not readily lend themselves to other forms of statistical analysis. The analysis of sparse observational data, which is called the population approach, has been implemented in phase III studies to obtain additional information about the PK/PD model. However, the primary purpose of phase III clinical trials generally is not PK/PD and consequently population PK/PD studies must be carefully interwoven with existing protocols.

**Key words**: drug development, pharmacokinetics, pharmacodynamics, sparse data.

**Correspondence:** Leon Aarons, School of Pharmacy and Pharmaceutical Sciences, University of Manchester, Manchester M13 9PL, U.K., Tel: +44-161-275-2357, Fax: +44-161-275-2396, Email: l.aarons@man.ac.uk

## INTRODUCTION

Pharmacokinetics, from the literal Greek meaning of the name, is the study of drug movement in the body. More specifically it is the study of the processes of drug absorption, distribution and elimination and frequently the definition is extended to encompass the relationship between plasma concentration and pharmacological effect, which more correctly is described as pharmacodynamics. Traditionally, pharmacokinetic studies have involved intensive experimentation in small groups of subjects, often healthy volunteers, in which a relatively large number of blood samples are withdrawn following drug administration. The design and analysis of such experiments is well established [1].

However consider the following data on tobramycin obtained during routine therapeutic drug monitoring [2]. Data from 97 patients (45 female, 52 male) were collected. The duration of therapy in individual patients ranged from 14 to 520 hr. 322 concentrations were available for data analysis with between 1 and 9 per individual (median 2). Drug concentrations were measured usually 2 and 6 hr after the dose in patients with normal renal function, with additional measurements (12 and 24 hr after the dose) in patients with impaired renal function. The age of the patients ranged from 16 to 85 yr, weight ranged from 42 to 120 kg and creatinine clearance ranged from 10 to 160 $ml.min^{-1}$. There are several points worth noting about this data set. Whereas in "conventional" pharmacokinetic study designs exclusion criteria are used to make the study population as homogeneous as possible (at least within a block) the population from the tobramycin study is very heterogeneous. No attempt was made to balance subject variables such as age, weight and renal function. The optimum pharmacokinetic model for tobramycin is the standard two-compartment model which involves four parameters. One does not have to be a statistician to realize that with, in some cases, only one plasma concentration per individual it is not possible to determine all four parameters. This sort of data is often referred to as **sparse**. Clearly there is information in the data but it is not possible to extract this information by conventional means, that is by investigating the parameters of each individual. To make progress one has to forget about individual analysis, at least to start with, and concentrate on the central tendency of the whole data, that is to determine the population pharmacokinetics.

*Population pharmacokinetics is the study into the pharmacokinetic similarity and* differences between individuals from measurements of drug levels in biological fluids of subjects or patients arising from some population of interest [3]. In contrast to a traditional study a population pharmacokinetic study involves large numbers of patients with very heterogeneous characteristics. Study control is difficult: many studies involve outpatients and many centres are involved. The reason for adopting a population approach to pharmacokinetic studies is that it has become increasingly obvious that one should study the drug in the target population, which may be different from a normal population. For example, pharmacokinetics may be altered by pathophysiological factors such as renal disease. In addition, apart from estimating mean pharmacokinetic parameters it is important to both quantify and explain interindividual variability, information which is important for the design of dosage regimens and therapeutic drug monitoring.

## TERMINOLOGY

Like all fields that bridge a number of disciplines, population pharmacokinetics is bedevilled by a mix of terminology and jargon. Some of the more common terms are defined here and, in the process, some aspects of data analysis are described.

**Population pharmacokinetics.** The study of the variability in plasma drug concentrations between individuals when standard dosage regimens are administered. Essentially the field deals with the exploration and quantification of trends in pharmacokinetic parameters as a function of patient characteristics: for example the dependency of renal clearance on renal function and volume of distribution on body size.

**Interindividual variability.** When applied to population pharmacokinetics, the average deviation of the drug concentration-time profile of an individual from the population mean.

This deviation may be explainable in terms of **covariates** such as renal function, age and weight.

**Intraindividual variability.** When applied to population pharmacokinetics, the residual variability in the drug concentration that is not explained by interindividual variability. The residual variability may be due to variability in the drug measurement, "biological" variability or to misspecifying either the pharmacokinetic model or the model describing the interindividual variability. These two sources of variability are contrasted in Figure 1.

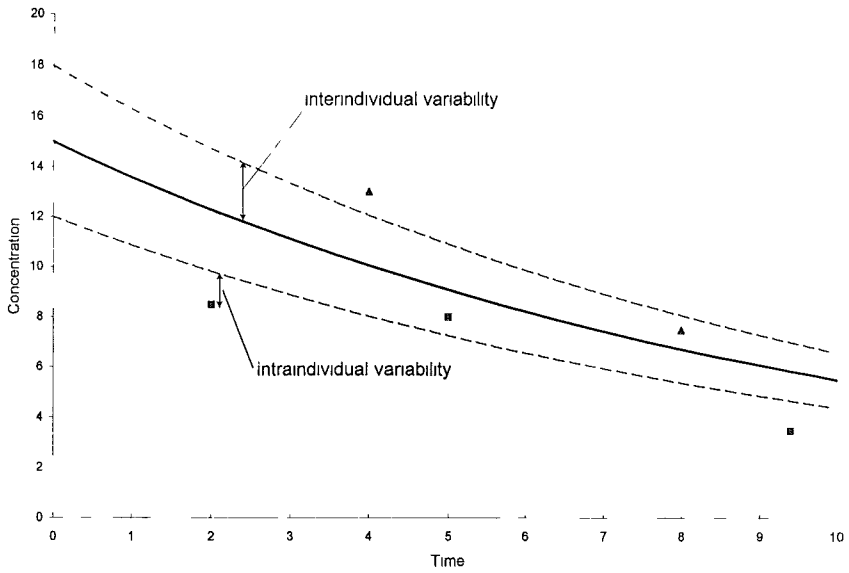


**Figure 1.** Sources of population pharmacokinetic variability. The solid line represents the "population mean" profile while the broken lines represent the individual profiles for subject j (data ▲) and subject k (data ■). The difference between an individual profile (at any time) and the mean profile is due to interindividual variability and the residual difference between the data and the individual profile is due to intraindividual variability.

**Population pharmacokinetic model.** The population pharmacokinetic model is a model that describes the drug concentration-time profiles of individuals within a population. It is comprised of two parts: a **structural model**, usually a conventional pharmacokinetic model, such as a one-compartment model, which may also involve covariates such as age and weight; and a **variance model**. It should be noted that the population pharmacokinetic model is not simply obtained by substituting the means of the pharmacokinetic parameters, obtained from fitting individual profiles, in the appropriate pharmacokinetic model.

**Variance model.** The variance model describes the difference between the drug concentration in an individual and that predicted by the structural model. The variance model may be a function of the pharmacokinetic parameters and covariates and in addition may involve other parameters. If the departure of an individual drug concentration from the population value is independent of concentration the variance model is said to be **additive.** On the other hand if the variance model is additive only after the structural model is log transformed, the variance model is said to be **multiplicative.**

**Some examples.** Consider a drug which can be described by a one-compartment pharmacokinetic model following iv administration, viz

$$C(t) = D/V*\exp[-CL/V*t]$$

where CL, the clearance, and V, the volume of distribution are the pharmacokinetic parameters. If in a population of patients receiving this drug the CL varies in proportion to renal function, as measured by creatinine clearance, $CL_{Cr}$, and the volume of distribution is proportional to body weight, then the pharmacokinetic model for the ith patient receiving a dose, $D_i$, would be

$$C(t) = D_i/(\theta_1*BWT_i)*\exp[-(\theta_2*CL_{Cr})/\theta_1*BWT)*t]$$

where $\theta_1$ and $\theta_2$ are the proportionality constants. The population pharmacokinetic model for the case where the inter- and intraindividual error terms are additive would be

$$C(t) = f(\theta_1,\theta_2,BWT,CL_{Cr},t)+\eta_i+\varepsilon_{ij}$$

where f is the concentration predicted by the model, $\eta_i$ is the difference between the population prediction and the prediction for subject i and $\varepsilon_{ij}$ is the residual departure of the predictions from the observations after accounting for interindividual effects. Normally the interindividual variability would be further partitioned into the contributions arising from the differences in pharmacokinetic parameters between individuals.

**Nonlinear mixed effects model.** A mixed effects model refers to a statistical model in which some characteristics are taken as fixed, that is known exactly, and others are assumed to be random. A nonlinear mixed effects model implies that the model is not a linear function of the parameters, which are to be determined from the data. Age and weight would be examples of fixed effects whereas inter- and intraindividual effects are random. The most widely known computer program in the area of population pharmacokinetics, **NONMEM** [4], implements a nonlinear mixed effect model (hence the name).

**Bayesian analysis.** If some population pharmacokinetic information is available from previous studies this **prior** information can be formally incorporated into the analysis of current data using Bayesian techniques [5].

## COMPUTER SOFTWARE

The analysis of data arising from a mixed effects model is not a trivial matter and requires sophisticated computer software. A number of approaches have been suggested [4-7]. An

expert meeting to discuss population pharmacokinetic/pharmacodynamic (PK/PD) software was held in Brussels in 1993 under the auspices of the European Co-operation in Science and Technology (COST), Medicine (B1) programme. The meeting developed from a successful conference (New Strategies in Drug Development and Clinical Evaluation: the Population Approach) held in Manchester in 1991 [8], also organized under the auspices of the COST B1 programme. The purpose of the Brussels meeting was to evaluate the present state of existing software and software under development; to specify the needs and wishes of potential users' of such software; and to integrate users' needs and software structures.

A full report of the proceedings of this meeting has been published [9]. The main message from the meeting was that the development of population software is an area of active interest. Already several very good packages are available and more are in development. There was general agreement that well validated, easy to use software was essential to the implementation of the population approach to drug development. The following is a summary of the important conclusions from the meeting.

- Software should be sufficiently user-friendly to allow an informed user to carry out population PK/PD analysis
- It is essential to be able to fully specify sparse data, including data arising from complex dosing histories
- Similarly it should be possible to specify pharmacokinetic and pharmacodynamic models in a completely flexible manner
- Good graphical diagnostics are essential for population analysis
- It is crucial that software is adequately supported and maintained.

## DESIGN AND PERFORMANCE OF POPULATION PK/PD STUDIES

The subject of the design of PK/PD studies was the subject of another COST-B1 meeting [10]. The purpose of the design meeting was to discuss current experience in the design and performance of population PK/PD studies. The main conclusions arising from the meeting were:

- When participating in the design of a new study, the population approach group must be careful not to include sampling or data collection items that would compromise the main objectives of the clinical trial.
- It is particularly important to communicate the purpose of the population PK/PD analysis to the investigators and to convince them of the importance of accurate timing and documentation.
- Some prior knowledge of the PK and PD models and covariate relationships is necessary for the analysis of sparse phase III data.
- Subject numbers are often dictated by the main objective of the clinical trial. However computer simulation and optimal design measures may be useful to define sampling times.
- Population methods must be specified in the protocol. Although population PK/PD analysis is often exploratory, the data analysis strategy should be specified as fully as possible.

## PHARMACOKINETIC SCREEN

The current interest in population pharmacokinetics was prompted by the concern that drugs, even drugs likely to be used in the elderly are not studied adequately in elderly patients and that as a consequence older patients are more likely than younger patients to suffer adverse drug reactions to drugs [11]. The FDA recommended that clinical trials should be conducted in target populations and the variability of the responses should be analyzed. During premarketing clinical trials, drugs should be subjected to a "pharmacokinetic screen". The spirit of the proposal was to look for unexpected phenomena and for large deviations in important features, such as side effects. Any finding should be followed up in subsequent, well-controlled trials. Sheiner and Benet [12] defined a number of ways in which this pharmacokinetic screen could be implemented.

1. A full pharmacokinetic study. This is the traditional approach of intensive sampling in a small number of subjects. As we have already remarked, this approach is not suitable for population pharmacokinetic studies.
2. Single trough screen. The number of subjects studied can be increased by reducing the number of samples taken per individual. The limit is one sample per individual and the obvious time to take this sample is just before a dose, that is a trough sample. Although such data can be analyzed by conventional ANOVA and the influence of covariates can be assessed, it provides limited pharmacokinetic information and does not allow the separation of intra- and interindividual variability.
3. Multiple trough screen. By taking more than one trough sample it is possible to partition intra- and interindividual variability, but such data still has limited pharmacokinetic information.
4. Full screen. If only a limited number samples can be taken for each individual than these samples should be spread throughout the dosing interval so that the data set viewed in its entirety maps out the concentration-time profile. Such designs allow the estimation of pharmacokinetic parameters and the separation of the different components of variability. The price that has to be paid is that sophisticated data analysis techniques have to be employed.

## THE CURRENT SITUATION

The last ten years has seen an increased activity in the area of population pharmacokinetics [8,13]. This interest was initially driven by therapeutic drug monitoring (TDM) and the need to make sense out of limited data [14]. However the methodology has now been applied to a wider range of problems. In particular the pharmaceutical industry has become aware of the advantages of analyzing data gathered during Phase II and III clinical trials, and it is apparent that a growing number of pharmaceutical companies are either actively investigating or are very interested in the use of population approaches in drug development [15]. Several issues need to be resolved:

1. Lack of trained personnel and user friendly software. These two go hand in hand. It is clear that the analysis of population pharmacokinetic data can not be treated as a hobby.

Staff have to be dedicated to population analysis and these activities need to be integrated into the drug development process.

2. Quality of data. Since much of the data generated during Phase III clinical trials is in outpatients there is a real concern about compliance and hence the quality of that data. Any solution that attempts to improve the quality of such data will inevitably incur a cost.
3. Experimental design and power. Experience with population approaches during drug development is increasing. However, so far only small scale simulation studies have been performed to investigate the optimal experimental design for the estimation of population pharmacokinetic parameters. Similarly little is known about the ability of population based approaches to detect important differences between subpopulations, that is to detect subpopulations at risk.
4. Selection of patients. Patients should be representative of patients receiving the drug. Certain subpopulations at risk should be preassigned and there should be a sufficiently large spread in important covariates such as age, weight, renal function etc.
5. The attitude of regulatory authorities. Regulatory authorities are aware of the interest in the area of population pharmacokinetics [16,17] but there is some concern about the acceptability of the approach. Recently the FDA has produced some draft guidelines for population pharmacokinetic studies [18].

## SUMMARY

One tends to be wary about adopting new approaches in an area which has well-established and validated methodology, particularly when there is little real experience with the new approach. The population approach is **not** a replacement for the conventional approach in drug development. Instead it is envisaged that the information from population analyses would complement and extend the information that is already being gathered. Indeed it is necessary to have a lot of baseline data on a drug - such as a good idea of the optimal pharmacokinetic model, an understanding of the metabolic pathways and some knowledge of the subpopulations that may have different pharmacokinetics - before embarking on a population study. This information would come from conventional studies.

Population pharmacokinetics should be viewed as a tool that can be used to extract meaningful information from clinical trial data that, up until now, has been largely discarded. The extra information available from such studies must increase the knowledge base of the drug and therefore must be worthwhile. However the cost/benefit ratio needs to be monitored. Above all there is an overwhelming need to study the pharmacokinetics of a drug in the target population as early as possible in a drug's development. It is unfortunate that the current controversy/debate has occurred since, on reflection, most scientists involved in drug development will realize that they are working towards the same goal.

In summary the following points need to be emphasized:

1. There are logistic and ethical problems involved in carrying out traditional intensive pharmacokinetic studies in large numbers of patients. Consequently only sparse data is likely to be available from such studies. These data have to be analysed in a statistically correct manner. To ignore the potential information in this data is both a waste of money

and is ethically unacceptable. A pharmacokinetic screen has been suggested as a means of implementing population pharmacokinetic studies.

2. Population based analyses should be viewed as exploratory in nature and therefore any unusual findings should be followed up by well controlled clinical trials. There is a risk of detecting false positives and therefore studies should be conducted in the light of the accumulated information and proceed in a sequential manner.
3. Although the nature of the drug development programme will not be radically altered by the advent of population based methodology there are expenses that will be incurred. Firstly a number of staff have to be dedicated to population analysis and these staff have to be trained. Secondly there is a need for quality data (one would argue that there is always a need for quality data). To ensure the quality of data gathered during Phase III clinical studies - compliance, dosing history and timing of samples - an extra level of monitoring may be necessary. Thirdly there is a cost for computing software and hardware. Interestingly enough, although much of the debate on population approaches centres around the computer programmes that are used, the costs of computing are much smaller than those of staff.
4. There are a number of studies that will, by their nature, only generate sparse data. These include studies in neonates, the acutely ill, field studies in the third world and frail elderly subjects.

## REFERENCES


1. Gibaldi M, Perrier D. Pharmacokinetics. 2nd ed. New York: Marcel Dekker, 1982.
2. Aarons L, Vozeh S, Wenk M, Weiss Ph, Follath F. Population pharmacokinetics of tobramycin. Br J Clin Pharmacol 1989; 28:305-314.
3. Aarons L. Population pharmacokinetics: theory and practice. Br J Clin Pharmacol 1991; 32: 669-670.
4. Beal SL, Sheiner LB. Estimating population kinetics. CRC Crit Rev Biomed Eng 1982; 8: 195-222.
5. Racine-Poon A, Smith AFM. Population models. In: Berry DA (ed.) Statistical Methodology in the Pharmaceutical Sciences. New York: Marcel Dekker, Inc., 1990, 139-162.
6. Mallet A. A maximum likelihood estimation method for random coefficient regression models. Biometrika 1986; 73: 645-656.
7. Lindstrom MJ Bates DM. Nonlinear mixed effects models for repeated measures data. Biometrics 1990; 46: 673-687.
8. Rowland M, Aarons L (eds.). New Strategies in Drug Development and Clinical Evaluation: the Population Approach. Luxembourg: Commission of the European Communities, 1992.
9. Aarons L, Balant LP, Mentré F, Morselli PL, Rowland M, Steimer J-L, Vozeh S. Population approaches in drug development. Report on an expert meeting to discuss population pharmacokinetic/pharmacodynamic software. Eur J Clin Pharmacol 1994; 46: 389-391.

10. Aarons L, Balant LP, Mentré F, Morselli PL, Rowland M, Steimer J-L, Vozeh S. Practical experience and issues in designing and performing population pharmacokinetic/pharmacodynamic studies. Eur J Clin Pharmacol 1996; 49: 251-254.
11. Temple R. Food and Drug Administration's guidelines for clinical testing of drugs in the elderly. *Drug Information Journal* 1985; 19: 483-486.
12. Sheiner LB, Benet LZ. Premarketing observational studies of population pharmacokinetics of new drugs. Clin Pharmacol Ther 1985; 38: 481-487.
13. Aarons L, Balant LP, Danhof M, Gex-Fabry M, Gundert-Remy UA, Karlsson MO, Mentré F, Morselli PL, Rombout F, Rowland M, Steimer J-L, Vozeh S (eds.). The Population Approach: Measuring and Managing variability in Response, Concentration and Dose. Luxembourg: Commission of the European Community, 1997.
14. Sheiner LB Beal SL. Bayesian individualisation of pharmacokinetics: simple implementation and comparison with non-Bayesian methods. J Pharm Sci 1982; 71: 1344-1348.
15. Jochemsen R. Current experience of population pharmacokinetics within the pharmaceutical industry: an introduction. In: Rowland M, Aarons L (eds.) New Strategies in Drug Development and Clinical Evaluation: the Population Approach. Luxembourg: Commission of the European Communities, 1992, 127-130.
16. Gundert-Remy UA. Population approaches in pharmacokinetics and pharmacodynamics - views within regulatory agencies: Europe. In: Rowland M, Aarons L (eds.) New Strategies in Drug Development and Clinical Evaluation: the Population Approach. Luxembourg: Commission of the European Communities, 1992, 153-156.
17. Peck C. Population approach in pharmacokinetics and pharmacodynamics: FDA view. In: Rowland M, Aarons L (eds.) New Strategies in Drug Development and Clinical Evaluation: the Population Approach. Luxembourg: Commission of the European Communities, 1992, 157-168.
18. http://www.fda.gov/cder/guidance/1852pk.htm

**Discussion: Population modelling**

**N. Benowitz:**
I was very curious about the statement that the FDA objected to the use of this modelling technique, because it was not planned as part of the analysis. Is there any bias that you can see in not planning this technique in advance?

**L. Aarons:**
I think they simply pointed out that 17% of cases were retrospective, and I am not sure that was an objection. The biggest problem they have is when someone has done the experiment and then he has asked the statistician to analyse the results. In this situation, the statisticians were never involved with the design of the experiment, and the chances of them being able to get a useful result out of it is fairly negligible. And the same is true here, if you are going to apply the method retrospectively, and it has not been designed appropriately, then the danger is that you really are not going to get useful information out of it.

**A. Breckenridge:**
My understanding of the European drug regulation authorities is that they have no objection to the use of population kinetics, provided it is backed up with a package of conventional pharmacokinetics. Is that your understanding as well?

**L. Aarons:**
I cannot answer that directly, but I can give you my opinion. Population PK/PD was never meant to replace traditional methodology, although in the early days it was thought to. It is another tool but it is not a panacea, therefore there is a place for the traditional Phase I studies. Now, how far should you go? There are situations where, in fact, data are not being analysed because they cannot be analysed by traditional methods. Therefore it is a tool which can analyse that data anyway. There are people who go a little further than that, and say that it is actually unethical not to analyse that data, with the provisos we just mentioned about design and so forth.

**T. Salmonson:**
Generally speaking, I think the lack of knowledge within regulatory agencies is greater in Europe than in the U.S., when it comes to population pharmacokinetic aspects. Having said that, I know that some companies are questioning if the FDA still is as favourable to the approach today as it was a number of years ago. In Europe it is regarded to be something to be used together with the standard package, not replace, which perhaps can give us additional information. I think it is also fair to say that few agencies do have statisticians or kineticists that can actually access this data. We are quite proud in Sweden to have that knowledge. The population approach is becoming more and more interesting from a regulatory perspective, but it is very slowly maturing in Europe compared to the US.

**J. Urquhart:**
One of the things that is striking in the contrast between PK and PD is that when you get into the PD side, you have what I call hard non-linear areas, which their reflection is the

dynamic asymmetries between on and off responses. You have some drugs like omeprazole that turn on quickly and go off very slowly, and others, like paroxetine, which go on very slowly and go off very rapidly. If you only have observations on the one side, you are in total darkness about what the other side is going to look like. There is a kind of a minimum data set that you have got to have, to be able to sketch out at least roughly the nature of those asymmetries, without which you are stuck when you come to making satisfactory models. You can do the PK side pretty nicely and project the time course of drug concentration, but you cannot project the damned actions because of the missing half of the sort of one-sided nature of PD's protocols, that leave you in the dark about off responses. I do not think there is any magic modelling technique that allows you to cut through that.

**L. Aarons:**

No, there is not. In fact, it comes back to the point about experimental design. With poor design you cannot get that information. So I agree entirely that if you do not have the data to allow you to do the appropriate modelling, then there is very little you can do, unless you have some prior information and can use Bayesian techniques to help you over the gaps in your data base. Perhaps it is also the reason I have got a problem with this term dose-dependent idiosyncratic responses, because I suspect they fall into this category you are talking about.

**M.M. Reidenberg:**

In doing just the PK work, it is my impression that the critical measurements are the time of drug administration, and then the time of sampling. You have shown that in the ICU 20% of cases had to be dropped. In other kinds of less rigorous settings, have there been studies on how accurate these recorded times are, and how much difference it makes with whatever degree of error is in the time recording?

**L. Aarons:**

It really does come back to recording accurately the dosing history and also the timing of the samples. I have not got any numbers that I can give you directly, but we are participating in a study to look at the impact of real compliance patterns, that is ones that actually have been measured in real settings, on the PK/PD analysis. So in the future we may have some answers for you.