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# Population pharmacokinetics: an overview

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## SUMMARY

The pharmacokinetics of a drug refers to how it is handled by the body. This includes absorption, distribution, metabolism and elimination.

Pharmacokinetic studies have usually been carried out in small numbers of people, often healthy volunteers. In population pharmacokinetics opportunistic samples are collected from actual patients taking a drug.

Population pharmacokinetic studies aim to identify and quantify sources of variability in drug concentration in the patient population. Associations between patient characteristics and differences in pharmacokinetics can then be used to customise pharmacotherapy, such as the safe use of metformin in patients with renal impairment.

As multiple samples from one person are not required, a population approach is useful for investigating patient groups that are difficult to study, such as premature infants.

Population pharmacokinetics is being increasingly used in drug development. It is particularly useful when it is suspected that the pharmacokinetics of the drug will vary between subgroups of the population.

## Introduction

The fundamentals of pharmacokinetics are crucial to understanding the biological fate of drugs. They are a cornerstone for good prescribing and drug development.[1]

Pharmacokinetics is concerned with the time-course of drug movement through the body. This involves the absorption, distribution, metabolism and elimination of drugs and their metabolites. These processes are described by mathematical models, which in many instances have been used in other disciplines such as biological chemistry (enzyme kinetics) and nuclear physics (exponential decay).

The study of pharmacokinetics has benefited immensely from advances in computer science and analytical chemistry. Pharmacokinetics can now be studied in populations of patients who are taking a drug. Studying a population enables the analysis of the variability in pharmacokinetics that occurs within and between patients. An example would be the variations in drug concentration which will occur with renal impairment when the patient is taking a drug excreted in the urine.

## Origins and development of population pharmacokinetics

It is routine practice to measure the concentration of drugs such as gentamicin. The population pharmacokinetic approach developed from the notion that improved prescribing could be achieved by the analysis of drug concentration-time data, typically produced from routine therapeutic drug monitoring. Population-derived pharmacokinetic parameters such as clearance could then be used to guide prescribing for individual patients.[2] Most importantly, this individualisation of therapy required the identification and quantification of various sources of pharmacokinetic variability such as weight, age, renal function and significant drug interactions.

Traditional pharmacokinetic studies usually involve multiple samples taken at fixed intervals from healthy volunteers. In contrast, population pharmacokinetic data are obtained from patients being treated with a drug. These patients are often taking different doses and have blood samples at different times. This unstructured and unbalanced dosage and blood sampling produces sparse response data (for example 2–4 samples per patient). A review of the various methods used in population pharmacokinetic analyses is provided elsewhere,[3] but the advantages and disadvantages of non-population and population methods are summarised in Boxes 1 and 2.

## Models and methods

Pharmacokinetic modelling is a mathematical method for predicting how a drug will be handled by the body. The term population pharmacokinetics almost always refers to 'mixed-effects' modelling. This is a mixture of fixed and random effects.

Fixed (structural model) effects are parameters such as clearance and factors that significantly influence clearance (for example weight, age). Random effects (variance model) parameters include the intersubject variability, and the variability which remains unexplained after fitting the model to the data.

### *Non-population methods* (Box 1)

In traditional pharmacokinetics studies, small numbers of people are intensively sampled over a given post-dose period using a fixed design. This is the so-called 'two-stage' approach. It is still widely used, for example in comparative bioavailability trials[4] and in clinical pharmacokinetics.[5]

In the first stage the values of the pharmacokinetic parameters (for example clearance) in each individual are calculated. The second stage involves estimation of descriptive statistics, usually the mean or geometric mean and standard deviation for each parameter. For example, the mean renal clearance of metformin is 510 +/– 130 mL/minute.

There are deficiencies with traditional studies, including the inability to handle sparse data and to identify which covariates, such as age and weight, are important sources of pharmacokinetic variability. The imprecision in estimating the parameter values is also unidentified when fitting the model to the data. This uncertainty leads to the interindividual variability being overestimated.

Another traditional method is the 'naïve pooled data' approach in which data from all participants are pooled as if they had been collected from one 'super-subject'. However, this approach ignores the sources of variability within and between individuals. It is not recommended even if there are numerous participants and the interindividual pharmacokinetic variability is relatively small.

### *Population methods* (Box 2)

A population pharmacokinetic method deals with modelling in a cohort which has many participants (usually more than 40). The population is studied rather than the individuals in it. Samples can be collected from patients taking different doses over different periods of time (see Fig.).

In population pharmacokinetics one may be interested, for example, in estimating a typical value of drug clearance or oral bioavailability. The typical parameter value is usually the mode (most frequently occurring value). This approaches the population mean value as the number of patients increases. However, the individuality of the information supplied by each patient to the population analysis is not lost, but is used to estimate the most likely value of a parameter for each patient. The reliability of these individual estimates is predicated on the amount of data contributed by each patient and by how much their estimated parameter value varies from the typical population value. In a sense, each patient lends information to the population model, but borrows information back from the population model to obtain an estimate of their own pharmacokinetic parameters.

There is a misconception that population pharmacokinetics is a fallback method for when there are only very sparse data, and that the ultimate aim should be to build models with as many covariates as possible. Neither of these views is valid. First, there is no substitute for data and while a population approach can handle sparse

#### *Box 1* Non-population pharmacokinetics

**Advantages**

- relatively small numbers of people are required (typically 8–16)
- sampling design is often fixed and therefore similar in all participants, so there is less potential for sampling errors
- pharmacostatistical concepts are familiar and may require only simple calculations

**Disadvantages**

- often performed in people who are not representative of the patient population
- infrequently performed in children
- multiple blood samples are required (typically >10 samples per person)
- pharmacokinetic variability between individuals is confounded with variability in the estimates of parameters such as clearance
- often cannot screen and quantify effects of covariates, such as weight, on pharmacokinetic response

#### *Box 2* Population pharmacokinetics

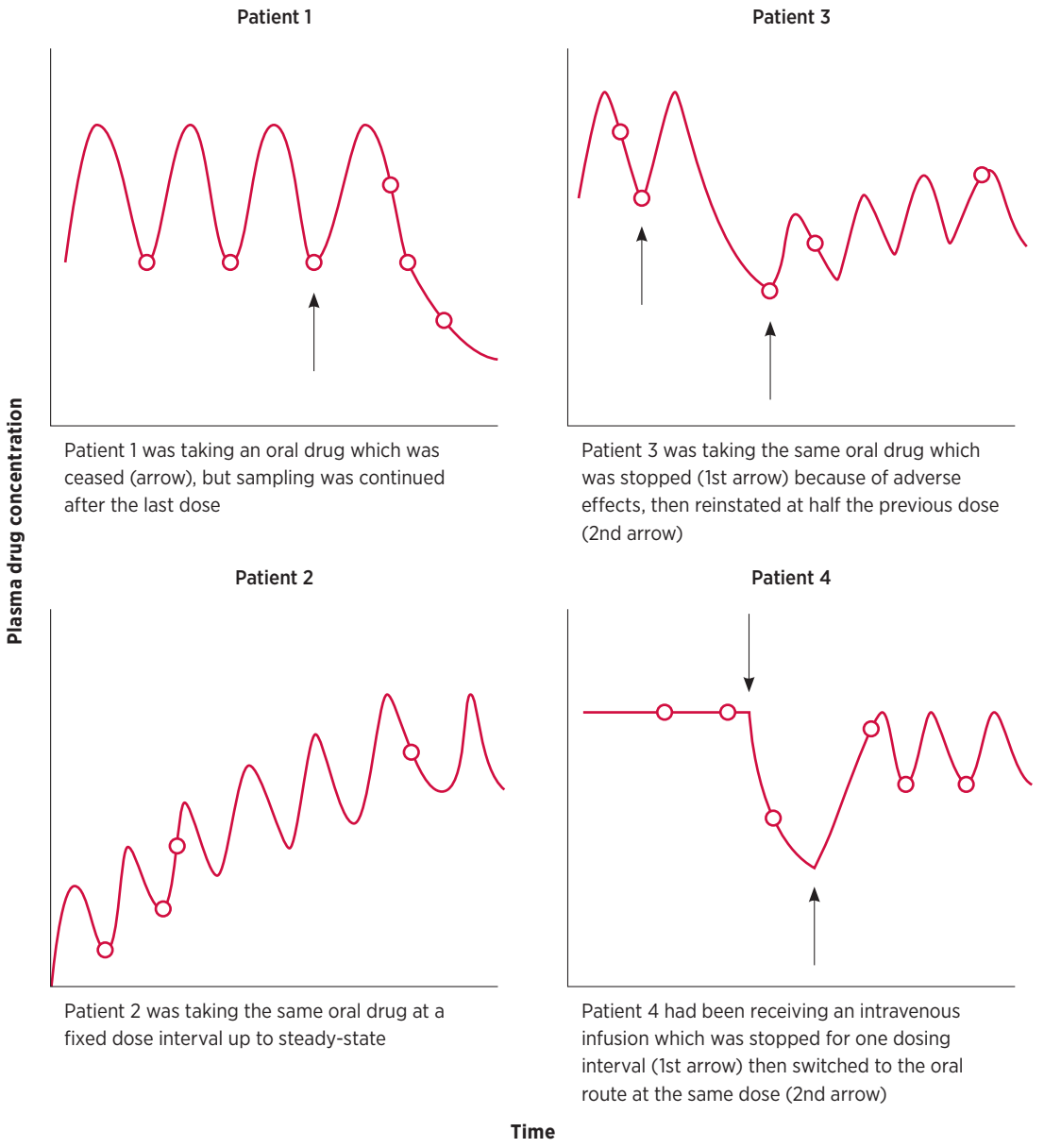
**Advantages**

- pharmacokinetic analysis is usually conducted in patients taking the drug
- can accommodate flexible study designs which occur during treatment
- only a few samples are needed from each patient
- opportunistic sampling has the potential to be cost-effective
- screening and quantification of covariates for explaining variability
- can distinguish between interindividual and intraindividual variability
- modelling software is widely available (e.g. NONMEM)

**Disadvantages**

- relatively large numbers of patients are required (typically >40)
- complex pharmacostatistical analyses
- requires collection, compilation and verification of large amounts of data
- model building may be tedious, labour intensive and time-consuming
- model diagnostics are often complex and time-consuming
- difficulties with handling missing data (e.g. all covariates in all patients)

*Fig.* **Examples of sparse blood sampling**




The figure shows four theoretical drug concentration time plots for different patients taking the same drug. It shows sparse blood sampling typically encountered in a population pharmacokinetic analysis. These profiles frequently involve different dosage regimens and different routes of administration (e.g. oral, intravenous) often with unheralded switching between routes in an unstructured and unbalanced pattern as clinical circumstances dictate.

observational data, there are limitations. For example, there should be more than one data point per patient, otherwise the interindividual variability becomes confounded (unidentified). Second, in the clinical context, it can be argued that a covariate should earn its place in a model only if its inclusion reduces the pharmacokinetic variability enough to warrant a change in prescribing. For example, renal function should be included when modelling the pharmacokinetics of gentamicin. Besides the problem of masking – in which two or more correlated covariates, for example weight and sex, can overlap in explaining a source of variability – complex models are harder to implement clinically and may increase the risk of prescribing errors.

## Application of population pharmacokinetic models

Population pharmacokinetic modelling is a complex activity.[6] It is also labour intensive and time consuming.

Like all mathematical models, a population pharmacokinetic model only provides estimates of the true (but unknown) pharmacokinetic parameter values. Fitting a model to the data results in some uncertainty in the true value of the estimated parameter, therefore plasma concentrations predicted by a model also have a degree of uncertainty attached to them. There is an oft-quoted adage that 'all models are wrong, but some are useful'. Population analyses have numerous useful clinical applications, especially in patients who otherwise may be difficult to recruit for a traditional pharmacokinetic study, for example young children or patients in intensive care.

Population pharmacokinetics is a much underused resource in Australia which could potentially improve clinical outcomes by informing individualised prescribing.[7] One example is the use of population pharmacokinetics to develop a dosage nomogram for caffeine in the treatment of infants with apnoea of prematurity.[8]

Another example is safely prescribing metformin for patients with impaired renal function. Using data from patients with various stages of renal dysfunction, a model was developed to identify and quantify the covariates, such as weight, which influence the pharmacokinetics of metformin. It then simulated dosage scenarios that could be used at various levels of renal dysfunction without the plasma concentration of metformin reaching a level which would result in adverse effects.[9] This work is valuable because it provided guidelines for using metformin in patients with renal impairment in whom the drug was previously contraindicated.

Population pharmacokinetic methods are an emerging and important part of drug development including preclinical studies, clinical trials and postmarketing surveillance. There are excellent reviews from the pharmaceutical industry[10] and regulatory perspectives,[11] and web-based guidelines from regulatory agencies.[12,13]

Studies have involved research and clinical applications in a wide variety of patients and conditions including diabetes,[9] clotting disorders,[14] malignancy,[15] serious infection,[16] apnoea of prematurity,[8,17] pregnancy,[18] organ transplantation,[19] self-poisoning[20] and arthritis.[21]

## Conclusion

The population pharmacokinetics approach is a powerful pharmacostatistical methodology for studying drug disposition under clinical conditions. It has major advantages over traditional methods of pharmacokinetics modelling, in that it can handle sparse data collected from unstructured and unbalanced dosing and sampling while facilitating a means of screening and quantifying sources of pharmacokinetic variability. Clinically, it has the potential to help the selection of the optimum dose for an individual patient. ◀

*Conflict of interest: none declared*

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