Design of pharmacokinetic – pharmacodynamic (PK–PD) studies in children: a workshop for health professions involved in paediatric drug research

Trevor N Johnson[1], Alison H Thomson[2]

[1] *Pharmacy Department, Children's Hospital, Sheffield, UK*

[2]*Department of Pharmaceutical Sciences and Department of Physiology and Pharmacology, University of Strathclyde, Glasgow, UK*

Corresponding author

Dr Trevor N Johnson, Pharmacy Department, Children's Hospital, Western Bank, Sheffield S10 2TH, UK.
E-mail: t.johnson@simcyp.com

A workshop on the design of pharmacokinetic-pharmacodynamic (PKPD) studies in children is described. The target audience was paediatricians, clinical pharmacologists, pharmacists, nurses, regulatory specialists and those with a range of roles in the pharmaceutical industry. Participants ranged in skill from those with significant expertise in PKPD to those with little or no experience in this area. The feedback from participants on the level and organisation of the workshop was positive. The workshop template can be modified to cover other aspects of PK and PD.

Paed Perinat Drug Ther 2006; 7:10–14

Keywords: children – education – pharmacokinetics – pharmacodynamics

Introduction

The word pharmacokinetics (PK) often strikes fear into people and they imagine pages of complex and unintelligible mathematical formulae. The modelling of pharmacodynamics (PD) or the time course of drug action linked to the PK merely adds to the panic. In reality, whilst a thorough understanding of the principles of PK (and PD) is imperative for conducting efficient and robust studies that have clinical and scientific credence, software packages are available that reduce the need for complex mathematical skills[1]. In designing such studies, a person experienced in PK–PD modelling who is proficient with one of the software packages should be included as part of the team.

There are two general approaches to conducting PK–PD studies. The classical approach requires a large number of measurements to be taken at fixed times from a small number of subjects. More recently, the use of population pharmacokinetic (POPPK) approaches has increased whereby a few (typically 1 – 4) blood samples are taken at various times from a large heterogeneous group of subjects. A comparison of the advantages and disadvantages of the two methods is shown in Table 1. The POPPK approach has a number of attractions for studying PK–PD in children; it is less invasive and can thus be considered as more ethical for this age group; blood sampling times are flexible and samples can therefore be taken to cause the least inconvenience to the patient and the least disruption to their clinical care.

A workshop is an ideal setting for teaching PK–PD in a professional conference setting as it can draw upon the experience of a range of expert participants. (It is useful to enrol such participants as breakout group leaders). Workshop tasks

Table 1 Comparison of the classical and population PK approach in paediatric drug research

Classical PK studies		Population PK studies	
Advantages	**Disadvantages**	**Advantages**	**Disadvantages**
Few subjects required	–	–	Larger population required
Relatively easy to control data recording	Requires intense blood sampling. May limit volume of each blood sample	Few blood samples required	May be difficult to ensure accuracy of data recording
–	Less ethically acceptable in children	More ethically acceptable	–
Detailed PK profile	–	–	Optimal sampling strategy required to obtain maximum information
–	More invasive for children	Less invasive, can be fitted around clinical procedures	–
Does not require specialist software	–	–	Specialist software required
–	More difficult to investigate the effects of covariates	More subjects required so can assess effects of a range of covariates	–
–	Cannot distinguish between inter-individual and residual variability	Can distinguish inter-individual, inter-occasion and residual variability	–

should be inclusive for those with less knowledge or experience and meaningful individual participation allows the audience to 'own' the subject and contribute to it. A number of different learning styles can be incorporated (exploration, instruction, practice and discussion) into the workshop structure.

Aim

The aim was to design a paediatric PK–PD workshop for the 3rd International Workshop on Paediatric Clinical Trials, Derby, UK. The likely audience would be paediatricians, clinical pharmacologists, pharmacists, nurses, regulatory specialists and those with a range of roles in the pharmaceutical industry. The range of PK–PD experience would be from expert (research/publications in area) to those with none or very little.

Structure of the workshop

Learning objectives

The workshop was entitled "Design of Pharmacokinetic-Pharmacodynamic (PK–PD) Studies in Children". The learning objectives were that by the end of the workshop participants should be able to:

- Describe how PK studies can be designed around the clinical care of children.
- Describe how PK studies can be conducted using a "sparse" sampling protocol.
- Describe methods for analysing data output from PK studies.
- Describe how PK can be linked to PD.

Two individuals acted as tutors for this workshop, which meant that presentation and supervisory roles could be shared and allowed a record to be made of answers and comments during the feedback session. Having two workshop leaders enabled questions to be answered from different perspectives, which helped to open up the discussion; it was also less stressful for the leaders, who could help each other out.

A. First presentation: Introduction to workshop – 10 minutes

In this section an overview of the workshop was given and the group task was introduced to the workshop participants along with some pointers as to how some of the questions/tasks should be approached. For example, for the question "How many patients will you include in your study?" The participants were asked to consider practicality, length of the study and how to obtain the maximum information.

B. Group task: design study protocol – 30 minutes

In this part of the workshop participants were split into four groups to undertake a guided task of designing a POPPK study. Known experts in POPPK or with experience in undertaking conventional PK-PD studies in children were split between the four groups. Groups were sent to different rooms to complete the task and workshop leaders were on hand to guide the groups and ensure they kept to the relatively tight time limits. The group task is described in Panel 1 and the questions to be addressed in Panel 2.

C. Group task: comments on study protocol – 20 minutes

Responses to questions presented in the workshop were fed back by the nominated person in each group. Responses and subsequent discussions were recorded and are summarised below.

Panel 1 Details of the group task

You have been asked to design a study to investigate the pharmacokinetics and pharmacodynamics of oral midazolam when used for sedation in children prior to surgery.

Background
- Midazolam is a benzodiazepine that is widely used to alleviate pre-operative anxiety in children who require minor surgical procedures. This is not a licensed indication.
- Oral doses are typically 0.5 mg/kg up to a maximum of 15 mg.
- The onset of sedation is 10 to 30 minutes and the typical duration of effect is 20 to 90 minutes.
- Midazolam undergoes extensive 1st pass metabolism (50%) after oral administration and is metabolised by CYP3A4 / 5 both in the small bowel enterocytes and in the liver. The mean elimination half-life of midazolam is between 30 minutes and 4 hours depending on age and study methodology.
- The major metabolite is 1-hydroxymidazolam, which has an elimination half-life of 1 hour and is also reported to have a sedative effect.
- Both drug and metabolite are excreted as glucuronide conjugates.
- More common adverse effects include prolonged sedation, ataxia, paradoxical agitation, hyperactivity and aggressiveness.

Setting
- The hospital where the study is to be performed has a busy day surgery unit with children attending for a variety of minor procedures - skin tags, ear correction, plastic surgery, hernia repair etc.
- Around 100 children per 6 months receive midazolam in the unit prior to their surgery.
- Ethical approval has been received to perform a population pharmacokinetic-pharmacodynamic study. A maximum of three blood samples is allowed per child.

Panel 2 Study design questions

General
- How could the study be designed around routine patient care?
- What is the ultimate aim of this study?

Data collection
- How many patients will you include in your study?
- When should blood samples be taken for PK analysis and who will take them?
- What should be measured?
- What patient information would you collect?
- What response (PD) measurements would you make and when? (Consider both therapeutic and adverse effects)

Data analysis
- How would you undertake the PK analysis – what factors do you need to consider?
- How would you undertake the PD analysis – what factors do you need to consider?
- How would you evaluate model performance?
- How would you evaluate your results or use them to design future studies?

How could the study be designed around routine patient care?

- Aim is to cause minimum disruption to clinical procedures but obtain maximum information.
- Pre-existing venous access will be available to allow administration of the anaesthetic. This means that a cannula does not need to be inserted for the purpose of the study, which is useful for both ethical and practical reasons.
- Disadvantages of designing a study around routine patient care include the potential effects of confounding variables, such as diet, co-morbidity, other drugs, etc. The effects of such co-variables can be included in the final POPPK analysis if a sufficient proportion of the subjects exhibit the variable.

What is the ultimate aim of this study?

- To obtain information that can be used to help design appropriate dosage regimens that optimise therapeutic response while minimising adverse effects.
- To provide information that would support a licensing application.

How many patients will you include in your study?

- Should we aim for 100 patients (or more) or would 50 patients be sufficient? In reality, for unbiased covariate analysis > 50 subjects are usually required.
- Consider practical issues. Is a study lasting 6 months feasible? In what proportion of the patients undergoing the surgery would we be able to obtain consent/assent for participation? Could the length of study be extended or should it be shorter?
- Consider how variable the patients are with respect to age, weight, other diseases, other drugs, etc. High variability will demand higher patient numbers to get useful results whereas low variability may allow the study to be conducted with fewer patients.

When should blood samples be taken for PK analysis and who will take them?

- As the dose is to be given orally, samples need to cover absorption and elimination phases.
- Do we need a pre-dose sample to ensure it is blank or does this just waste information and pose ethical problems related to the

volume of blood withdrawn? What volume of whole blood and serum/plasma is required for the assay?
- Define sampling windows to allow flexibility in sampling, i.e. ideally sample at 0–1 hour, 1–2 hours and 2–3 hours in each patient. Use optimal sampling theory to design the sampling protocols. The general technique is to use prior PK data along with D-Optimality sampling methods to define a sequence of sampling times that provides the most information for the PK parameter estimates by minimising their standard error estimates. The development and implementation of sampling strategies in POPPK analysis has recently been reviewed[2].
- Consider practical issues. To avoid interference (or interactions) with other drugs going through the line, take samples at the beginning and at the end of the procedure. The anaesthetist can take the samples. Where will they be stored and for how long will they be stable? Can they be analysed as a batch at the end of the study? Will an assay method (and staff) be available at the appropriate time?

What should be measured?

- Both drug and metabolite concentrations and PD.

What patient information would you collect?

- Age, weight, height (size), sex, hepatic function before and after administration, other drugs, other disease states, renal function.

What response (PD) measurements would you make and when? (Consider both therapeutic and adverse effects)

- Sedation score preferably using a validated scoring system performed by a suitably trained anaesthetist. However, a simpler scoring system could be used which matches what you are trying to achieve in the study. In the case of this study, awake/anxious vs drowsy/asleep may be sufficient.
- How should adverse effects be recorded and analysed? For example, list adverse effects and score as present / absent at different times, e.g. half-hourly intervals up to 3 or 4 hours.

How would you undertake the PK analysis – what factors do you need to consider?

- Exploration of the initial data (e.g. by examining scatterplots to look for outliers) before modelling begins.
- What pharmacokinetic models will you test for drug and metabolite? How will they be parameterised? Consider what models can be used to describe variability in parameters between patients and residual error in the concentration measurements.
- Software – need to perform a population analysis since the data are sparse, e.g. use: NONMEM, Kinetica, PPharm, WinNonMix.
- A population analysis allows you to use all the data – even if some samples have been missed from some patients and only one measurement is available.
- Where do the initial parameter estimates come from, e.g. other paediatric studies, extrapolation from adult data? May also come from the results of a naïve pooled data analysis.
- What covariates should be included in the PK analysis? Are they correlated (e.g. age and weight)? What order will they be entered into the model or will you try all combinations? How will you correct for size, e.g. use an allometric weight model for clearance? How should covariate effects be modelled – do you need to consider both linear and non-linear relationships?

How would you undertake the PD analysis – what factors do you need to consider?

- As you have categorical response data, you could model the probability of the score by logistic regression considering drug concentrations alone, metabolite concentrations alone, the sum of drug and metabolite concentrations.
- Do you need to consider other factors, such as other drugs, other clinical characteristics, etc?
- Should the PD be monitored sequentially or simultaneously? It is generally agreed that sequential analysis (develop a PK model first and then link the model to a PD model) is as good as simultaneous.

How would you evaluate model performance?

- This was not discussed in the workshop but could be included the future. Discussion may revolve around statistical (e.g. F-test, Akaike information criteria) and more visual methods (e.g. residual plots, observed *vs* predicted plots) to evaluate model performance.

How would you evaluate your results or use them to design future studies?

- Use the results to predict concentrations and response in future patients and compare with actual concentrations and response.

- Use the results to simulate how future clinical trials should be conducted.
- Use the results to develop new dosage guidelines, introduce the guidelines and monitor clinical outcome/response.

D. Short presentation on completed study – 10 minutes

The workshop was based on a study previously undertaken by Johnson et al.[3]. Emphasis was placed on areas where the study could have been improved. (Some of this information had already been highlighted in the group feedback session.)

Brief summary of original oral midazolam study

Oral midazolam is widely used for pre-operative sedation in children. The aim of this study was to investigate the pharmacokinetics and pharmacodynamics (sedation score) of both midazolam (MDZ) and its active metabolite 1-hydroxymidazolam (1OHMDZ).

Two blood samples were collected at random times from 45 children (age 9 months to 12 years) prior to anaesthetic induction and at end of the surgical procedure. The study was designed around the clinical procedure, as children already had a cannula *in situ* for collecting blood samples and were asleep or sedated. A simple and practical sedation score (1 = awake, 2 = drowsy / asleep) was recorded at the same time as the first blood sample. The population-PK software P-Pharm (version 1.5, SIMED, France) was used to analyse the MDZ and 1-OHMDZ data and included the effects of a number of covariates including age, weight, sex and metabolic ratio (1-OHMDZ/MDZ). The PK-PD modelling of the sedation score in relation to plasma MDZ and 1-OHMDZ was carried out using logistic regression analysis.

Despite large variations between individual patients, predicted plasma MDZ and 1-OHMDZ concentrations from the final POPPK model were very close to the observed data. The best PK-PD model included both MDZ and 1-OHMDZ as active moieties and predicted the correct sedation scores in 86% of cases. 1-OHMDZ has approximately 50% of the activity of MDZ and can compensate, at least in part, for the decreased effect of the parent compound due to its increased metabolism in young children. The POPPK–PD results regarding the sedative effects of 1-OHMDZ were consistent with classical PK–PD studies performed in adults[4,5]. The most important observation was that a median dose level of 0.5 mg/kg MDZ resulted in an odds ratio of 4 in favour of score 2 *vs* 1, and suggested that a 50% increase in dose would be necessary to achieve sedation in almost all subjects. However, the authors emphasised that the safety of this dose increase would have to be further evaluated.

Discussion

The overall template for this workshop can be adapted according to the aims and objectives as well as the audience. For instance, a rich data PK study could be selected for the basis of teaching in this area. Other areas that could likewise be covered include basic PK principles, clinical trial simulation, specific PK-PD software packages, allometrics and therapeutic drug monitoring. The workshop provides a non-threatening atmosphere in which participants can learn PK-PD without being overwhelmed by statistical principles and to show what can be done with the correct techniques and approaches. A recent paper by Meibohm et al.[2] gives a more detailed overview of some of the issues in designing and analysing POPPK studies in paediatrics. Overall, the organisers received positive comments from the participants on the structure and content of this workshop.

References

1. Aarons L. Software for population pharmacokinetics and pharmacodynamics. Clin Pharmacokinet 1999;36:255-264.
2. Meibohn B, Laer S, Panetta JC, Barrett JS. Population pharmacokinetic studies in pediatrics: Issues in design and analysis. AAPS Journal 2005;7:1-24. Also at http://www.aapsj.org/view.asp?art=aapsj070248
3. Johnson TN, Rostami-Hodjegan A, Goddard JM, Tanner MS, Tucker GT. Contribution of midazolam and its 1-hydroxy metabolite to preoperative sedation in children: a pharmacokinetic-pharmacodynamic analysis. Br J Anaesth 2002;89:428-437.
4. Mandema JW, Tuk B, van Steveninck AL et al. Pharmacokinetic-pharmacodynamic modelling of the central nervous system effects of midazolam and its main metabolite α-hydroxymidazolam in healthy volunteers. Clin Pharmacol Ther 1992;51:715-728. AAPS Journal 2005;07:1-24. Also online at http://www.aapsj.org/view.asp?art=aapsj070248
5. Ziegler WH, Schalch E, Leishman B, Eckert M. Comparison of the effects of intravenously administered midazolam, triazolam and their hydroxyl metabolites. Br J Clin Pharmacol 1983;16:63-69S.

PPDT 0143, *Accepted for publication:* 21 December 2005
Published Online: 22 March 2006
doi:10.1185/146300905X65731