Paediatric Clinical Research Infrastructure Network

Procedures for the setup of neonatal trials

Sampling techniques for neonatal pharmacokinetic studies: Points to consider

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Description	This tool provides practical points to consider for neonatal pharmacokinetics studies
Key words	Neonatal trial, Protocol development, Guidance document, Tool, Pharmacokinetics

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Inserm

Disclaimer: **Sponsors and researchers unfamiliar with clinical trials in neonates and/or neonatology are advised to seek expert advice due the complexity of neonatology.**

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Introduction

Currently, one of the major challenges in neonatal clinical drug trials is that information supporting a given dose may be limited or non-existent. Therefore, a pharmacokinetic (PK) study may need to be conducted prior to any efficacy or safety trial. Conducting PK studies in neonates is challenging because obtaining biological samples (e.g. blood, urine, cerebrospinal fluid) is technically difficult, limited by the volume that can be obtained and the frequency and timing of such samples.[1-5]

Whilst PK studies can be conducted using a variety of biological samples (e.g. cerebrospinal fluid, urine, saliva), neonatal PK studies usually use blood samples.[5] Neonates have only a very small circulating blood volume (about 80 to 90 ml/kg body weight).[2,6] Routine clinical care of neonates aims to keep the number of invasive procedures, such as blood testing, to an absolute minimum.[2,7] Consequently, the number and volume of PK blood samples which can be specifically drawn for a neonatal PK study are limited.[1,5] Due to these limitations it is not feasible to conduct traditional pharmacokinetics studies in neonates.[1,8]

European guidelines for clinical trials in neonates recommend that for an individual neonate:[2]

"the trial-related blood loss (including any losses in the manoeuvre) should not exceed 3 % of the total blood volume during a period of four weeks and should not exceed 1 % at any single time."

Therefore, opportunistic and scavenged sampling methods are frequently used in neonatal PK studies.[9]

Innovative population pharmacokinetic studies: scavenged samples

Sometimes the terms of opportunistic and scavenged sampling are used interchangeably. Recently the Food and Drug Administration (FDA) defined:[5]

- scavenged samples as "samples obtained from surplus blood drawn during of clinical care"
- opportunistic sampling as "sampling around the time of clinically indicated blood draws"

Scavenged samples and opportunistic sampling are used in neonatal PK studies in order to reduce study related interventions, associated risks and distress.[5,8] With careful planning and execution opportunistic and scavenged sampling methods can be as precise as traditional PK sampling.[1,5]

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The challenge of planning neonatal PK studies is the inter- and intrainduvidual variability of drug response in neonates.[5,10] It is therefore important to understand the ontogeny of the target tissues as well as the ADME (absorption, distribution, metabolism, excretion) of the active ingredient, its metabolites and excipients, where applicable.[5,10-14] In addition, it is key to understand how different neonatal subpopulations respond to the study drug, for example those with intrauterine growth restriction.[5] Therefore, the data collection in neonatal PK studies needs to be carefully planned and should be based on modelling and simulation.[5,15-18]

The sparse data obtained from these studies should be analysed using population PK analyses.[3,7,9,15] Population PK is the study of the variability in drug concentration between individuals of the target population receiving a standard dose.[4,5,7,10,18] It includes the analysis of factors which influence the interindividual variability of drug concentrations.[4,5,10,16,18]

Requirements for neonatal pharmacokinetic sampling

The following points should be considered when obtaining samples for neonatal PK studies:[5,19,20]

- Analyses needed for routine clinical care take precedence over any PK analyses if the sampling volume is low
- PK samples are obtained prospectively at random times after drug administration
- The number of PK samples per patient and study cannot be predefined in the protocol
- Accurate data on the timing of study drug administration and sampling are critical, thus detailed planning in collaboration with the personel taking the samples is required
- Storage and sample processing need careful consideration; this may include stability testing in routine care (e.g. sample not processed for a prolonged period [e.g. during the weekend], storage under extreme conditions [e.g. temperature, humidity, phototherapy])

An example of a form for an opportunistic or scavenged PK blood sample for an intravenous drug is provided in Figure 1.

Conclusions

Neonatal population PK studies can reduce study related risks (e.g. blood loss; pain) by using opportunistic and scavenged sampling methods. Accurate data collection of the time and dose of drug administration and sampling time are essential for successful neonatal PK studies. Sponsors and researchers unfamiliar with neonatology and/or neonatal pharmacology are advised to seek expert advice.

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Competing interests

All authors consider not having any competing interests for this tool. BA has worked for GlaxoSmithKline between October 2006 and September 2009 and holds company shares. Between October 2009 and May 2015 she has worked for Novartis.

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Figure 1. Innovative population pharmacokinetic studies: Scavenged samples – Example of a form for an opportunistic or scavenged PK blood sample for an intravenous drug

Opportunistic or scavenged pharmacokinetic (PK) sampling information sheet

Study drug:	**Study title:**	**Study number:**

Study centre number:

Patient study identifier (Study ID):*

Study drug administration

Dose number	**Dose (i.e. in mg or mcg)**	**Date**	**Start time of infusion (0:00 to 23:59)**	**Stop time of infusion (0:00 to 23:59)**
1				
2				
3				
…				

Opportunistic or scavenged PK sampling

Sample number	**Date**	**Sampling time (0:00 to 23:59)**	**Sample:**
1			1. One each tube indicate clearly • Patient Study ID • Study centre • Sampling date • Sampling time 2. Please follow study instructions for handling the sample.
2			
3			
…			

Page 1/1	Date of sending the sample:

*** Please note that the study ID is different from the patient's hospital number.**

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