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LETTER TO THE EDITOR

Comment on Pharmacokinetic Studies in Neonates: The Utility of an Opportunistic Sampling Design

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Over the last decade, neonatal pharmacokinetic (PK) studies have increasingly been conducted to support the licensing of medicines in this vulnerable population. It is sometimes proposed that opportunistic sampling (also known as scavenged sampling), where drug concentrations for PK analysis are measured in leftover routine samples regardless of time relative to dose, is the most practical method to obtain PK data in neonates. However, regulatory advice states that sponsors are expected to objectively justify the sampling scheme [1]. Consequently, we were delighted to read of an effort to address neonatal PK study design with a comparative analysis (opportunistic sampling, timed sampling and pooled combined sampling) undertaken by Leroux et al. [2] on their recently published, ciprofloxacin neonatal PK data [3].

Leroux and colleagues report that dosing conclusions would have been the same whether timed, opportunistic or all data had been used; therefore, advocating the inclusion of opportunistic samples in neonatal PK studies. We suspect they are somewhat over-enthusiastic in interpreting their data. This was a single-drug study run at two centres in the same city under the auspices of a European FP-7 project with what could be described as optimal resources. Whether inference from this work could be applied to multicentre studies, studies on other drugs with different PK profiles or studies in resource-limited settings is questionable. Furthermore, of potential concern are the raw data presented in Fig. 1 of their paper that show a different trend in the concentration-time course of the timed and opportunistic samples, indicating a possible systematic error in the opportunistic data.

The model parameter estimates for disposition differed substantially for opportunistic and timed samples with V_1 being fourfold lower and Q threefold higher; this is despite timed and opportunistic samples having been taken in the same patients. When increasing the richness of the data by pooling timed data with the opportunistic samples, uncertainty measured by relative standard error (%) counter-intuitively increased in all PK parameters except clearance, which stayed the same. The authors explain this by stating opportunistic samples were clustered at certain times in the dose interval, but this does not seem to accord with visual inspection of the raw data, nor explain why parameter precision would decrease. Goodness-of-fit for the opportunistic data under the timed model and vice versa would have helped tease out whether the opportunistic data were simply uninformative or systematically different.

A recent quinolone PK/pharmacodynamic model suggests that the shape of the concentration-time profile independent of area under the plasma concentration-time curve (AUC) is important, with higher maximum plasma concentration (C_{max}) for the same AUC limiting the development of resistance [4]. In Fig. 1, we have plotted the typical curves for opportunistic, timed and all data, showing that the opportunistic curve has a C_{max}

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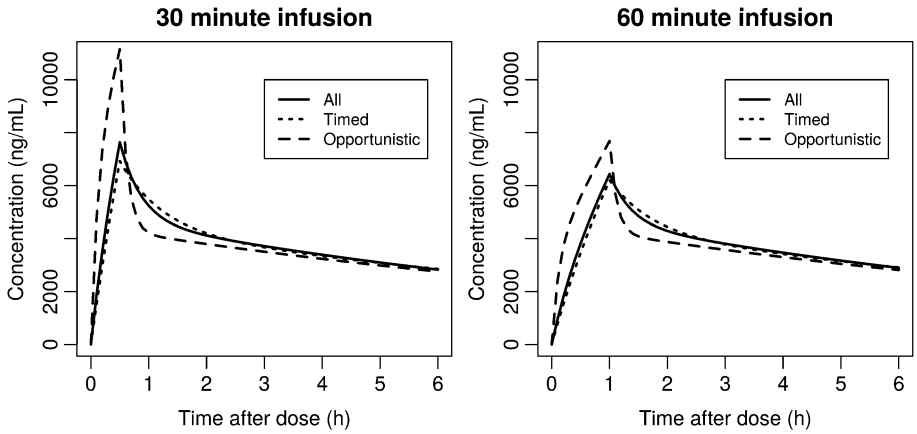

Fig. 1 Pharmacokinetic profile for a typical patient weighing 1995 g, a gestational age of 27.9 weeks, a post-natal age of 27 days, a serum creatinine of 42 μmol/L and not receiving inotropes for the models derived from the timed data, opportunistic data or pooled data. Plot on the *left* shows the 30-min infusion, plot on the *right* shows the 60-min infusion

approximately 25 % higher than the timed model if given over 60 min, or over 60 % higher if given over 30 min. Because the timed sampling model was developed using data capturing C_{max}, one would assume the timed profile is correct and fortunately there were more timed than opportunistic samples; therefore, the opportunistic data did not dominate the shape of the pooled fit. The timed samples give a good prediction of the whole PK curve, and in an era of increasing resistance, this more nuanced approach to antimicrobial pharmacokinetics/pharmacodynamics will increasingly be used to derive dosing guidelines.

Leaving aside these dispositional differences, in this particular example with this particular spread of opportunistic samples, Leroux et al. did find similar clearance with opportunistic and timed sampling. Because their dose recommendation was based on AUC, another equally valid conclusion is that the opportunistic samples were unnecessary (and potentially caused the inclusion of an incorrect covariate by adding unexplained variability to the pooled model), so perhaps the timed samples alone would have sufficed.

The dilemma faced by study designers is that optimally timed samples will always be more informative on PK model parameters (and methods to define optimal times have long been established for paediatric studies [5]), yet investigators and parents wish to decrease study invasiveness by taking the minimum number of samples co-ordinated with routine tests wherever possible. It is therefore important that PK samples are only taken when necessary, and that each sample is optimally informative.

As Leroux et al. point out, neonates in intensive care undergo frequent routine blood tests, so arranging for some of these to be taken at times that give optimal PK information should be possible. This can be achieved by moving routine blood test timing to coincide with optimal PK times or shifting dose times so that optimal sampling times match planned routine blood sampling. Balancing information loss with practicality can be further explored at the design stage by defining sampling windows rather than fixed times for some or all samples [6]. We encourage investigators to aim for neonatal study designs where all PK samples are taken at optimal times, wherever possible combined with routine blood samples, and to bear in mind that regardless of study design, accurate recording of dosing and sampling time is essential.

Compliance with Ethical Standards

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