Commentary

Pharmacotherapy during neonatal extracorporeal membrane oxygenation: toward an evidence-based approach

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See related research by Van der Vorst *et al*., http://ccforum.com/content/10/6/R168

Abstract

Van der Vorst and coworkers recently illustrated the large variability in furosemide regimens used in their unit. This finding at least suggests that we need more data on the pharmacokinetics and pharmacodynamics of this drug in neonates during treatment with extracorporeal membrane oxygenation, in order to ensure quality of care and safety, and to promote evidence-based prescription. The implementation of population pharmacokinetic models can further increase both the feasibility of such studies and the relevance of the results generated.

Although the general principles of clinical pharmacology apply to neonates and young infants, the characteristics of this population warrant a specific approach. The relative body water content, fat distribution and muscle mass are markedly different in foetal than in neonatal and paediatric groups. Almost all phase 1 and phase 2 hepatic clearance processes have a distinct isoenzyme-specific ontogeny, whereas renal clearance in early neonatal life is limited and depends almost entirely on glomerular filtration rate; the result of these factors is that the body's clearance of pharmacological agents evolves in a drug-specific, age-dependent manner. Extracorporeal membrane oxygenation (ECMO) further affects the pharmacokinetics and pharmacodynamics (PK/PD) of drugs. It is therefore mandatory that population-specific data in neonates on drug-specific PK/PD during ECMO be collected in order to ensure quality of care and safety, and to promote evidence-based prescription.

Recently in *Critical Care*, Van der Vorst and coworkers [1] described the Rotterdam group's experience on the administration of intravenous furosemide to neonates undergoing ECMO. The authors report considerable variability in furosemide regimens used without any benefit from additional bolus administration in their cohort, using urine output during the first 24 hours after initiation and time to reach 6 ml/kg per hour as pharmacodynamic outcome variables.

The appropriateness of initiating ECMO in neonates with respiratory insufficiency has been firmly established by the UK-ECMO trial [2], but data on the PK/PD of drugs that are frequently prescribed in these neonates are less robust. Van der Vorst and coworkers [1] correctly identified that the retrospective design of their study prevented them from drawing definitive conclusions, but they highlighted a need for a prospective PK/PD study to evaluate a predefined continuous furosemide regimen. Population pharmacokinetics provides clinical researchers with a potent tool with which to improve both the relevance and the feasibility of studies on developmental pharmacology in neonates.

Population modelling using mixed effects models provides a means to study variability in drug responses among individuals who are representative of those in whom the drug will be used clinically. These models have advantages for paediatric studies for the following reasons: they can be used to analyze sparse data; sampling times are not crucial; they can be fitted around clinical procedures; and, finally, individuals with missing data may still be included. Covariates account for the predictable component of the variability between individuals. Growth and development are two major aspects in children that are not seen in adults. These aspects can be investigated using size and age as covariates [3,4].

Mulla and coworkers [5,6] recently reported on the pharmacokinetics of midazolam and vancomycin using population modelling. They identified important changes in both clearance and volume of distribution of these drugs during ECMO treatment, in addition to the normal changes in these factors that would be expected to occur with age and

ECMO = extracorporeal membrane oxygenation; PK/PD = pharmacokinetics and pharmacodynamics.

maturity. Similar trends were documented by Peters and coworkers [7] in their evaluation of morphine pharmacokinetics during venoarterial ECMO in neonates. In general, there is an increase in distribution volume, which is most prominent in water soluble drugs, and a decrease in drug clearance.

Whether to initiate any treatment is a decision balanced by a cost-benefit consideration based on potential effects and side effects. The use of furosemide has been associated with nonconductive hearing loss at age 5 to 8 years; continuous administration of furosemide necessitates additional intravenous access; and there remains uncertainty regarding pharmacodynamic end-points [1,8]. We therefore strongly agree with Van der Vorst and coworkers [1] that there is a need for a prospective PK/PD study on the use of furosemide in neonates during ECMO. The hearing loss associated with furosemide use suggests that long-term follow up is needed in neonates who have undergone ECMO treatment, and the implementation of population pharmacokinetic models can further increase both the feasibility of such studies and the relevance of the results obtained, as illustrated by the work of Mulla [5,6] and Peters [7] and their groups.

Following documentation of the advantages of using ECMO to manage neonatal respiratory insufficiency in terms of both mortality and morbidity, the evaluation of pharmacotherapy during neonatal ECMO should become a second step toward a more evidence-based approach to these patients.

Competing interests

The authors declare that they have no competing interests.

References

1. Van der Vorst MM, Wildschut E, Houmes RJ, Gischler SJ, Kist-van Holthe JE, Van der Heijden AJ, Burggraaf J, Tibboel D: **Evaluation of furosemide regimens in neonates treated with extracorporeal membrane oxygenation.** *Crit Care* 2006, **10:**R168.
2. Petrou S, Bischof M, Bennett C, Elbourne D, Field D, McNally H: **Cost-effectiveness of neonatal extracorporeal membrane oxygenation based on 7-year results for the United Kingdom Collaborative ECMO trial.** *Pediatrics* 2006, **117:**1640-1649.
3. Anderson BJ, Allegaert K, Holford N: **Population clinical pharmacology of children: general principles.** *Eur J Pediatr* 2006, **165:**741-746.
4. Anderson BJ, Allegaert K, Holford N: **Population clinical pharmacology of children: modelling covariate effects.** *Eur J Pediatr* 2006, **165:**819-829.
5. Mulla H, McCormack P, Lawson G, Firmin RK, Upton DR: **Pharmacokinetics of midazolam in neonates undergoing extracorporeal membrane oxygenation.** *Anesthesiology* 2003, **99:** 275-282.
6. Mulla H, Pooboni S: **Population pharmacokinetics of vancomycin in patients receiving extracorporeal membrane oxygenation.** *Br J Clin Pharmacol* 2005, **60:**265-275.
7. Peters JW, Anderson BJ, Simons SH, Uges DR, Tibboel D: **Morphine metabolite pharmacokinetics during venoarterial extra corporeal membrane oxygenation in neonates.** *Clin Pharmacokinet* 2006, **45:**705-714.
8. Robertson CM, Tyebkhan JM, Peliowski A, Etches PC, Cheung PY: **Ototoxic drugs and sensorineural hearing loss following severe neonatal respiratory failure.** *Acta Paediatr* 2006, **95:** 214-223.