



Paediatric Clinical Research Infrastructure Network

Procedures for the setup of neonatal trials

Excipients in neonatal medicines: Points to consider

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Description	This tool provides a check list of points to consider for excipients in neonatal formulations
Key words	Neonatal trial, Protocol development, Guidance document, Tool, Excipients

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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

Medicines prescribed to neonates need to have a favourable benefit-risk balance including a formulation adapted to the neonatal population which, for example, limits the risk of medication errors and does not contain excipients which are known to be harmful. Neonatal formulation development is challenging due to rapid maturational changes which may influence pharmacokinetics (PK) and/ or pharmacodynamics (PD), a heterogeneous patient population, common polypharmacy; as well as limits on fluid volume, flow rate of administration, excipients considered to be safe and route of administration. An additional challenge is that the formulation may need to be manipulated to suit neonatal dosing requirements, which may increase the risk of medication errors, lack of efficacy and toxicity.

Points to consider for excipients used in neonatal formulations

The metabolic capacities of neonates, and in particular of premature neonates, are not the same as those in older children or adults.^{1,2} This does not only concern the metabolism of the active moiety of a medicine but also the excipients.^{1,3} Due to the developmental immaturity of neonates excipient thresholds considered safe for adults or older children may be harmful for neonates. There is currently limited data on the neonatal safety of many of the excipients included in adult medicines.^{1,3} However, several excipients, such as benzyl alcohol, are known to be unsafe in neonates.^{1,3,4} In addition, many neonates are often treated with several other medications which may have the same excipients as the study drug. Thus the recommended daily threshold for one or more excipients may be exceeded.^{4,5,6} Finally, interactions between different types of excipients may lead to toxicity.⁷ Due to the vulnerability of the neonatal population it is recommended to aim for formulations with as little excipients as possible and ideally none at all.^{4,8} The current knowledge on excipients in paediatric medicines is available from the Safety and Toxicity of Excipients for Paediatrics (STEP) database.^{9,10} Examples of points to consider for excipients in neonatal formulations are listed in [Table 1](#).

Conclusions

Medicines used for treating neonates should have an age appropriate formulation to ensure safe prescription, preparation and administration and only include excipients which are tolerated by neonates. Researchers are advised to seek expert advice if a medicine needs to be adapted for the neonatal population in order to ensure best practice is used for its preparation and that an effective and safe dose is administered.

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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Table 1. Check list of points to consider for excipients used in neonatal formulations (not exhaustive)

Excipients in neonatal formulations: Examples of points to consider	Considered	Not considered	Not applicable	Comments/ notes
Current data on excipient pharmacodynamics ¹⁻³				
Current data on excipient pharmacokinetics ¹⁻³				
Current data on excipient toxicity threshold ¹⁻³				
If the excipient has a known toxicity threshold: estimate additional exposure from same excipient in comedications (check SPCs of common comedications in target population and calculate average, minimum and maximum exposure for relevant exposure duration [e.g. 24 hours and weekly] ^{4,5}				
Current data on short-term toxicity ¹⁻⁴				
Current data on long-term toxicity ¹⁻⁴				
Current data on risk of accumulation with repeat exposure ^{2,3}				
Current data on interactions with other excipients ^{2,3,6}				
SPC= Summary of Product Characteristics (=Product information/ label) References: <ol style="list-style-type: none"> Valeur KS, Holst H, Allegaert K. Excipients in Neonatal Medicinal Products: Never Prescribed, Commonly Administered. <i>Pharmaceut Med.</i> 2018;32(4):251-258. doi: 10.1007/s40290-018-0243-9. European Paediatric Formulation Initiative (EuFPI). Safety and Toxicity of Excipients in Paediatrics (STEP), [internet], November 2018. Available at: https://step-db.ucl.ac.uk/eupfi/appDirectLink.do?appFlag=login Salunke S, Tuleu C; European Paediatric Formulation Initiative (EuFPI). The STEP database through the end-users eyes - USABILITY STUDY. <i>Int J Pharm.</i> 2015 Aug 15;492(1-2):316-31. doi: 10.1016/j.ijpharm.2015.06.016. Valeur KS, Hertel SA, Lundstrøm KE, Holst H. The Cumulative Daily Tolerance Levels of Potentially Toxic Excipients Ethanol and Propylene Glycol Are Commonly Exceeded in Neonates and Infants. <i>Basic Clin Pharmacol Toxicol.</i> 2018 May;122(5):523-530. doi: 10.1111/bcpt.12950. Akinboni TO, Davis NL, Falck AJ, Bearer CF, Mooney SM. Excipient exposure in very low birth weight preterm neonates. <i>J Perinatol.</i> 2018 Feb;38(2):169-174. doi: 10.1038/jp.2017.165. Food and Drug Administration (FDA). Drug safety communication: serious health problems seen in premature babies given Kaletra (lopinavir/ritonavir) oral solution. 2011, Washington DC. Available at: https://www.fda.gov/drugs/drugsafety/ucm246002.htm 				