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COMMENTARY

Substitution as a Strategy to Improve Excipient Exposure in Neonates: One Piece of the Puzzle

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1 Introduction

Since extensive variability is the key characteristic of neonatal pharmacology despite an overall low elimination capacity, this should translate in drug formulations to *low*, *adjustable* and *flexible* dosing to maintain dose accuracy. This observation is not limited to the active compounds, but also applies to excipients [1, 2].

In this issue of the journal, Nellis et al. quantified the potential impact of systematic product substitution within Europe as a strategy to reduce exposure to potentially harmful excipients (i.e. parabens, polysorbate 80, propylene glycol, benzoates, saccharin sodium, sorbitol and ethanol) in neonates [3]. The authors hereby explored the between-country variability in exposure to excipients in formulations administered to 726 neonates in 21 different European countries. Using availability of the same active pharmaceutical ingredient with a similar dosage form (but not similar strength/concentration) as prerequisites, substitution potentially resulted in a relevant reduction in number of prescriptions (from 638 to 317 out of 2095 prescriptions) containing these excipients, with an important decrease in number of exposed neonates (from 456 to 257 out of 726 newborns).

We value the potential of substitution. However, we suggest that such a strategy can only be part of a broader strategy to improve the practices related to excipient exposure in neonates since implementation of systematic substitution is not straight forward to incorporate in daily clinical practice. The current paper was a theoretical 'in silico' modelling effort rather than a 'real-world' scenario. As the authors already mentioned, substitution comes with its own problems, including economic (e.g. lack of reimbursement, additional shipment costs), regulatory (e.g. international transport, responsibilities of national authorities, physicians or pharmacists, validity of national product registrations) and logistics-related (e.g. product storage, differences in concentrations) issues. Moreover, only a qualitative, dichotomous (present/absent) and not a quantitative excipient exposure has been used in the current exercise [3]. Extrapolating from experience on substitution built from product shortages, we should be aware that the real-life setting of product replacement is potentially less supportive for such a strategy.

To illustrate these burdens, we refer to the experience reported on component shortages for parenteral nutrition in a survey on this issue conducted by the Institute for Safe Medication Practices (ISMP) [4]. Based on 234 respondents (pharmacists, pharmacy staff), medication errors and adverse outcomes were observed by at least 20 % of the responders. Observed errors mentioned by the responders were confusions between paediatric and adult products,

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mix-ups, differences in concentration with alternative products, or errors in changes to be made to protocols, templates, work labels, compounders and order entry systems. A relevant number of respondents (68 %) had experience with the import of products into the United States after the Food and Drug Administration (FDA) utilised its discretion to ease shortages of critical components. Besides additional expenses, differences between products and—related to this—the need for manipulations and steps to prepare and dispense the products to individual patients, were commonly reported. Other concerns related to compatibility, stability or sterility [4].

This survey puts the strategy to reduce excipient exposure in neonates through 'simple' product substitution by import into another perspective. Despite this, we still consider the Nellis paper of relevance when integrated into a systematic strategy to improve neonatal pharmacotherapy [3]. Such a systematic strategy should focus on awareness of excipient exposure in neonates throughout the lifecycle of a product to generate information [2].

To attain safe and effective pharmacotherapy for infants, the clinical characteristics of newborns and the pharmacokinetic estimates of a specific compound should be considered. In general, clearance in neonates is low. As a consequence, neonates are in urgent need of tailored drug product development that considers the need for both low and flexible dosing to maintain dose accuracy. During the development of such formulations, there is also a need for guidance on excipient exposure. We hereby should be aware that excipients established for 'adult' formulations may be inappropriate for use in neonates because of maturational pharmacokinetics (differences in exposure) or pharmacodynamics (differences in effects and side effects) of these excipients [2]. Consequently, each excipient considered for use in neonates should be justified in terms of safety and appropriateness. This is knowledge that goes beyond a single compound or manufacturer similar to, for example, food safety approaches, and there is a need for a systematic strategy of knowledge integration [2].

2 Avoid the Avoidable

Although this concept seems simple, it does need out-of-the-box thinking, similar to the substitution suggested by Nellis et al. [3]. At least, the fact that different formulations with and without potentially harmful excipients exist throughout Europe strongly suggests that there is a possibility to further explore the variability in practices between, but perhaps also within, countries. Unfortunately, most of the currently available summaries of product characteristics (SPCs) only provided qualitative and not quantitative information on the excipients in specific formulations. Despite this, the current paper provides circumstantial evidence that excipient-free formulations are sometimes possible. For Pharmacy and Therapeutics Committees involved in determining a hospital's drug formulary, we also suggest that they consider the quality of formulations, including excipients, when discussing uptake of new drugs in the formulary, especially in cases of intended neonatal or paediatric use. Finally, acceptability of mini-tablets as a strategy to avoid excipients (e.g. taste masking, alcohols, preservatives) in neonates has also recently been reported [5].

3 Try to Learn from Current Practices to Estimate Safe Levels of Exposure

The available knowledge on the safety or toxicity of excipients is perhaps limited, but certainly even more difficult to retrieve. An important initiative to improve this setting is the Safety and Toxicity of Excipients for Pediatrics [STEP] database initiative [6, 7]. This is a knowledge-sharing platform constructed following a survey on potential users, their toxicity and safety information needs and their ideas about the content and structure for the database [6]. Following its development, a 'usability' study on the STEP database through end users has been conducted to further improve its availability [7]. One may use the setting of existing clinical exposure to different excipients to quantify developmental pharmacokinetics or pharmacodynamics. This concept has been proven to be feasible through, for example, the propylene glycol research project and the European Study for Neonatal Excipient Exposure (ESNEE) initiative (parabens, ethanol) [8, 9]. Interestingly, these studies also documented that differences in pharmacokinetics were not limited to the extent (lower), but were also found in routes of elimination. In contrast to adults (55/45 %), propylene glycol is eliminated almost exclusively by hepatic metabolism (85 %) with only minor contribution of urinary elimination (15 %) in neonates [10]. Ethanol is also metabolised more extensively to acetaldehyde in neonates [11].

4 Do Not Forget Future Drug Development

The drug development process will likely not be limited to new compounds, but will also generate new excipients. Consequently, toxicity studies should also include excipient studies in juvenile animals, such as Poloxamer 188 [12]. We hereby suggest careful consideration of both the active compound and the excipients, since there is anecdotal evidence of synergism between the active compound

and the excipient (e.g. phenobarbital and propylene glycol) [13].

In conclusion, the field of developmental pharmacology of excipients in neonates is growing and evolving. In our opinion, the suggestion of substitution is only one piece of a broader strategy to further improve current practices, since this should cover prevention, knowledge gathering and building.

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Compliance with Ethical Standards

Conflict of interest K. Allegaert and I. Spriet declare that they have no relevant conflicts of interest.

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