Evidence-based prescribing for children can be challenging because of insufficient data on safety and efficacy, and a lack of suitable formulations. What is being done to address these issues?

Time to strengthen the evidence base for paediatric formulations

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In the era of modern medicine, the need for data on clinical efficacy and safety for a given medicine is not questioned. Despite this, medicines use in children remains an area that, largely, lacks sound evidence for a variety of reasons (see Box 1).

**Formulation is important**

Adult formulations are often unsuitable to use for children; many children are unable to swallow adult tablets or capsules and the available strengths can be inappropriate.

In practice, the lack of child-friendly preparations means that pharmacists are often required to manipulate available dosage forms; this leaves a greater potential for dosing errors and adverse events, resulting in poor overall therapeutic outcomes. For example, cutting tablets, even using commercially available tablet cutters, can produce pieces that contain as little as 50% or up to 150% of the desired dose.

An area of particular concern is extemporaneous conversion of adult tablets or capsules into liquids for children. This is commonly achieved by deconstructing tablets or capsules and dispersing the resulting powder in a suspending agent.

This process can produce a more acceptable preparation for children and remains an essential part of paediatric pharmacy practice. However, the resulting formulations are rarely assessed for their pharmaceutical quality — shelf-lives are often set arbitrarily, with little or no evidence to support the physical, chemical or microbiological stability of the preparations.

Moreover, the crude suspensions described below. Difficulties with trial design

Well designed formulations, appropriate drug presentation (active drug and matching placebo) and effective drug supply processes are all critical to the authorisation and success of clinical trials.

**Formulation research**

The Medicines for Children Research Network (see Box 2, p29), in collaboration with three academic centres (Aston University, Birmingham; John Moores University, Liverpool; and The School of Pharmacy, University of London), has established a formulation workstream to concentrate on paediatric formulation issues. The workstream’s main activities are described below.

**Describing the problem**

The workstream aims to determine the scope of and identify the specific issues arising from the lack of appropriate paediatric formulations. These investigations will enable priority setting for targeted research to ensure viable, cost-effective research programmes that include all aspects of paediatric medicines.

**Difficulties with trial design**

Well designed formulations, appropriate drug presentation (active drug and matching placebo) and effective drug supply processes are all critical to the authorisation and success of clinical trials.
Problems with formulation are often identified late in the trial protocol review process and can lead to delays, mounting costs and subsequent complications in the conduct of the trial and the interpretation of the results. Furthermore, failure to develop a formulation that is robust (in terms of stability and bioavailability) before starting a trial can mean that the trial results are not applicable to clinical practice.

Early scrutiny of formulation-related issues, ideally at the point of protocol development and feasibility assessment, is therefore essential in achieving efficient trial set-up. The workstream provides feedback on protocol issues such as formulation (eg, appropriateness of dosage form, safety of excipients and dosing accuracy) and stability (eg, shelf-life, in-use stability and compatibility with food or vehicles), as well as assistance with sourcing of active or placebo investigational products and trial packaging.

Extemporaneous preparation

The problems associated with extemporaneously prepared medicines used for children are being examined, first through engaging with patients, carers, prescribers and pharmacists to determine a definitive picture of the issues experienced in practice. In addition, a priority list of formulations is undergoing thorough pharmaceutical assessment. This work is being conducted to inform current practice and develop improved paediatric formulations through, for example, the selection of alternative, age-appropriate excipients. The extemporaneous formulations that have been prioritised for investigation are those that:

- Are used to treat chronic disease
- Have a critical indication
- Are high risk or can cause toxicity

Development

Research into novel dosage forms and exploitation of existing and emerging drug delivery technologies are also key activities of the workstream. Examples include the use of alternative dosage forms such as minitablets, chewable tablets, orodispersible tablets and powders for reconstitution, or innovative designs such as oral wafers.

Bottom line

Providing evidence for acceptable, safe, feasible and age-appropriate dosage forms for children is a challenge for the scientific community. The MCRN (and, in particular, the formulation workstream) is striving to improve the evidence base through effective and focused research involving clinicians, academia and the pharmaceutical industry.

References


Box 2: What is being done to improve the evidence?

Problems with the development and availability of safe, effective and acceptable medicines for children are well recognised and the World Health Organization has a global campaign to “make medicines child size”. Within Europe, introduction of the 2006 Regulation on medicinal products for paediatric use (EC) No 1901/2006 means that, in addition to conducting adult studies, new medicines must undergo trials in children. However, companies can apply for a waiver in cases where the new medicine would not have a paediatric indication (eg, Alzheimer’s disease). Incentives are offered to companies for conducting these trials (eg, six-month patent extensions). Regulatory bodies are also offering 10-year data protection and market exclusivity for the introduction of paediatric formulations of existing off-patent medicines through a “paediatric use marketing authorisation” (PUMA).

In the UK, in anticipation of this legislation, the National Institute for Health Research created the Medicines for Children Research Network (www.mcrn.org.uk) in 2005 to facilitate the growing demand for paediatric clinical trials. The MCRN aims to improve the co-ordination, speed and quality of randomised controlled trials and other well designed studies of medicines for children and adolescents, including those for prevention, diagnosis and treatment.

The knowledge and experience of the MCRN allows it to provide advice and assistance regarding the conduct of paediatric clinical trials in the UK. This is being achieved through collaboration with:

- The NHS
- Academic institutions
- The pharmaceutical industry
- Consumers

The MCRN supports industry-sponsored and investigator-led studies in over 100 NHS sites in England that serve around 6 million children.