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Editors' view

Paediatric prescribing: why children are not small adults

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Prescribers today find themselves in a much more difficult position than has even been the case in the entire history of medicine. Not only do they have available to them more drugs to treat more diseases than ever before, but the types of drugs and their modes of action are becoming ever more complex. One important consequence is that the potential for adverse drug events is greater than it has ever been, and we have written about this problem extensively in the pages of this journal over the last few years.

This issue is difficult enough in adult medicine, but the problem is compounded in paediatrics, and especially so in neonatology, due to a number of considerations. Many drugs exhibit very different pharmacokinetics in children compared with adults, at all levels of drug disposition (absorption, distribution, metabolism and excretion). Medication adherence in children is highly dependent on the drug's formulation, taste, appearance and ease of administration, as well as factors specific to the parents or carers (including their own medication beliefs and perceptions of risk *vs.* benefit). Importantly also, many medicines are used in paediatric practice outside the terms of their marketing authorization (licence). Most medicines used have only been formally tested for safety and efficacy in adults, and comparatively few medicines are available on the market which are specifically licensed for the treatment of children. It is against this backdrop that we have considered it timely to publish a themed section on paediatric prescribing. The papers in this section cover many of these issues as well as others relevant to the use of medicines in children.

Joseph and colleagues [1] review the issues surrounding clinical trials of medicines in children. A major reason for medicines being licensed in adults only is that, until relatively recently, there has been a widespread reluctance to conduct studies of medicines used in the treatment of children due to ethical concerns as well as practical and commercial considerations. In recent years this has been changing and, with an increasing international recognition of the need for good quality clinical trials in children, coupled with the development of new initiatives and regulations to cover such trials, the authors call for increased funding as well as infrastructure to support these.

The ethical and practical issues specifically associated with clinical trials of medicines in neonates are addressed by Turner [2]. Neonatal care units have a particular culture in their practice which needs to be taken account of in the design and conduct of such trials, and close involvement of parents at all stages from design to conduct is imperative. Turner argues that, with appropriate adaptations which take into account all of these factors, trials in neonates should be no more challenging than in other age groups – and that, indeed, there is an ethical imperative to conduct good quality trials of medicines in the neonatal population.

A particular challenge is posed by the development of biologics for use in children. As pointed out by Smith and colleagues [3], these agents have made an enormous impact in the treatment of a wide variety of autoimmune conditions in children, just as in adults. However, their assessment to date has largely relied on randomized control trials using a withdrawal design, rather than a parallel study design, due to ethical concerns including use of placebo treatments in children with active disease. This design, however, poses important limitations and problems as regards data reliability and safety assessment. The authors point to the need for national and international collaboration for delivery of biologics registries and long term, open label studies, in order to gather robust data on safety and efficacy of these agents.

As discussed above, multiple physiological and anatomical differences give rise to pharmacokinetic disparities in children compared with adults. These are discussed by Batchelor & Marriott [4]. Obtaining good quality pharmacokinetic data is crucial to determining

appropriate dosing régimes in children, and especially so in children less than 2 years old, since this group exhibit the greatest differences from adult pharmacokinetic profiles and at the same time it is in this group that pharmacokinetic data are least likely to be obtained in clinical trials. Since most efficacy and safety data are obtained in adults, extrapolating from adults to children requires robust pharmacokinetic modelling based on good quality data. However, in children there are limitations on blood sample volumes that can be taken and there are also worries about causing pain and discomfort from venesection. The authors discuss alternative sampling techniques such as saliva and urine sampling and finger/heel pricks that can minimize the invasive nature of such trials and also discuss how population-based modelling can help to reduce the number of samples required from each individual within a population by increasing the overall population size.

In a separate article, Batchelor & Marriott also discuss how differences in formulations for paediatric products (not only for administration by mouth but also by other routes) can give rise to unexpected drug pharmacokinetic profiles with resultant changes in both efficacy and safety [5]. The problem is compounded by the fact that, in almost one in five cases, patients or their carers further manipulate medicines to aid adherence. The authors highlight the need for evidence-based information to guide the development of formulations that are appropriate and acceptable to children and young people, which give the desired pharmacokinetic profile. Furthermore, the implications of manipulating their medicines need to be carefully explained to patients and their families.

Personalized medicine, largely based on pharmacogenetics/pharmacogenomics, is very much an area being researched and exploited both within academia and the pharmaceutical industry and in some areas of adult medicine, has already made significant impact. In the paediatric arena, however, it is still very much a science in its infancy. Sing and colleagues review what has been achieved in paediatric pharmacogenomics, and discuss its current limitations and challenges as well as approaches to how these may be overcome in the future [6].

In this context, the paper by Vu and colleagues is especially timely [7]. Acute lymphoblastic leukaemia is the commonest malignancy of childhood and, although 80% of cases are curable using modern therapies, survival varies between different racial and ethnic groups, which may in part be attributable to polymorphisms in drug metabolizing enzymes. The authors determined the presence of a number of such polymorphisms in a cohort of Caucasian and Vietnamese patients with acute lymphoblastic leukaemia and used these data to calculate a multilocus genetic risk score. Their data demonstrate that including this score into a clinical model improved the predictive accuracy of short and medium term prognosis in this disease.

For the clinician practising adult medicine, the British National Formulary has been an invaluable guide, not just in the UK but internationally, since its inception in 1949. In view of the difficulties associated with giving good guidance on paediatric prescribing, no similar guide existed for children's medicines until relatively recently. Lenney charts the history of the British National Formulary for Children [8], starting with the publication of 'Medicines for Children' in 1999 which in turn led to the first edition of the British National Formulary for Children in 2005, all the way to the present day.

One particular area of paediatric prescribing which is of particular importance and concern is that of antibiotic use in low and middle income countries, where infectious diseases remain the leading cause of death in childhood. This area is discussed by Le Doare and colleagues [9]. The problem arises largely as a result of inappropriate prescribing or dispensing of antibiotics, coupled to the fact that many patients do not take prescribed antibiotics correctly and is further compounded by the continuing global rise in antibiotic-resistant organisms. The authors discuss the barriers which exist to rational prescribing of, as well as access to, antibiotics for children in low and middle income countries, as well as global initiatives which have been developed to address these barriers.

Together, these papers give insights into many important facets of medicines use and prescribing in children, and show that indeed, in case we did not already know it, children are not just small adults.

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