Editors' view

Paediatric special issue

N. S. Baber, Medical Manager, Medicines and Healthcare products Regulatory Agency, London, UK

Email: nigel.baber@mhra.gsi.gov.uk

The British Journal of Clinical Pharmacology is pleased to dedicate this month's issue to the clinical pharmacological and therapeutic aspects of paediatric medicine. The backdrop to this is now familiar to most physicians with an interest in the use of medicines in children. There is widespread recognition across Europe and in the USA that the discovery, development, regulation, and clinical use of medicines specifically for children are in a parlous state. The reasons have been well rehearsed, and include lack of commercial interest, ethical and practical difficulties in conducting studies in children, an inadequate understanding of the effects of age and development on the pharmacodynamics and pharmacokinetics of drugs, and inconsistent responses by regulatory authorities to the challenge of assessing paediatric studies. The complexity that these issues impose on attempts to conform to the norms of pharmaceutical and regulatory medicine, which have been established in adults, is being addressed by governments, regulators, clinicians, and industry.

An impressive start has been made in the USA, with the establishment of Clinical Research Centres [1], dedicated to clinical trials in children, and by the introduction by the Food and Drug Administration (FDA) of exclusivity legislation [2, 3]. The latter is not, however, without problems. In order to maintain equality of opportunity in the market place, a company can apply for a period of exclusivity for its paediatric and adult medicinal products, provided the paediatric studies meet sufficient standards of design and analysis. Not surprisingly, commercial opportunism has taken precedent over clinical need, and several products in the same therapeutic class, for example antihypertensive drugs, have been brought forward when some older and more useful drugs would have been preferable.

Europe has been slower to start but is rapidly catching up. The Paediatric Expert Group, a subcommittee of the Committee on Human Medicinal Products at the European Medicines Agency (EMA), has undertaken an impressive programme of reviews of the efficacy and safety of a number of therapeutic classes of paediatric medicines and the availability of paediatric formulations. It is also developing new guidelines on pharmacodynamic and pharmacokinetic studies in children. The European Commission is actively working on new legislation modelled on the FDA's strategy, so that Companies that make new product applications will have to include a paediatric development plan (unless there is no clear paediatric indication) and will have to undertake evaluable studies, in return for which a period of exclusivity will be granted [4]. Legislation is also being developed to encourage companies to conduct clinical trials on 'old products' that lack an appropriate formulation, or for which there is no licensed indication.

The UK has also made some very significant and exciting advances on a broad front. The Government has established a National Service Framework on Children's Health [5]. The Medicines and Healthcare products Regulatory Agency (MHRA) has a Paediatric Working Group, a standing subcommittee of the Committee on Safety of Medicines (CSM) which gives regular advice on the safety and efficacy of medicines for children, with the aim of establishing either more licensed indications or advice on the summary of product characteristics (SPC) to help prescribers. Getting closer to home, the Royal College of Paediatricians and Child Health has published a landmark report on the development of a clinical and research base for paediatric pharmacology in the UK [6], which recognizes the need for training more paediatric clinical pharmacologists, establishing posts, and setting up a Clinical Research Network

(UKCRN). The Department of Health has recently announced the launch of the Medicines for Children Network as part of the UKCRN, with its co-ordinating centre in the Institute of Child Health, Liverpool. The first call for expressions of interest to become a local research network was made in April 2005 [7].

The British National Formulary is preparing a dedicated paediatric formulary, to be launched later this year. The British National Formulary for Children (BNF-C) will draw on the wisdom of its parent and the excellent publication 'Medicines for Children' [8].

This journal has always welcomed papers on paediatric issues with a clinical pharmacological or therapeutic theme. In the last three years we have published about 40 papers related to medicines in children, but this is the first issue dedicated solely to papers on paediatrics.

Real progress towards safer and more effective medicines designed for children can only occur by collaboration between industry, academia, and regulators. To that end, the MHRA and the Paediatric Working Group of the CSM instigated a tripartite meeting entitled 'Towards establishing optimal doses for drugs prescribed to children'. The Association of the British Pharmaceutical Industry (ABPI) hosted the meeting, at which short papers were presented, followed by discussion. A summary of the major contributions is published in this issue of the *Journal* (pp. 660–2).

The main source of new medicines that receive regulatory authorization is the pharmaceutical industry, and more specifically 'Big Pharma'. Rose (pp. 657–9) reviews the challenges facing the industry in developing specific paediatric programmes and throws down the gauntlet to health authorities that investment in modern methods, such as virtual trials simulation, must be acknowledged as part of the development process. He also raises the controversial issue of whether pharmaceutical companies should be represented on the Paediatric Board to be established in the new European Paediatrics strategy. Baber (pp. 660–2) reviews the current European and FDA guidelines to industry concerning dose optimization in children. In addition there are two guidelines on the use of pharmacokinetics and dynamics and on formulation development, in the consultation stage. Together all these should provide enough scope for the inclusion of newer methodologies, as well as the traditional approaches to dose optimization.

There are two approaches to the prediction of doses in children, namely allometric scaling and physiologically based pharmacokinetic modelling (PBPK). Early optimization of dose ranges in children, as in adults, is either undertaken by the classical approach, in which

many measurements are taken at fixed times from a small number of subjects, or by the sparse data sampling or population pharmacokinetic approach (POPPK), in which small numbers of measurements are taken at random from a large heterogeneous group of subjects. It is unlikely in the foreseeable future that *in silico* predictions will replace clinical studies for new drugs, but as Johnston points out (pp. 663–9), their successful application could provide the best scientific approach for decision making and selecting first-time doses in children and in aiding study design. The Centre for Drug Evaluation and Research (CDER) has already recognized the need to be practical in taking best evidence from adult studies and mixing and matching with specific paediatric phase I trials [9]. Johnston describes the development of a PBPK database, built on knowledge of organ maturation (weight and volume) and the ontogeny of drug elimination pathways, which will allow comparisons of predicted and real (though sparse) pharmacodynamic and pharmacokinetic variables. Using oral midazolam he and his colleagues were able to show, despite large variations between individuals, a close correlation between the predicted and actual plasma concentrations of midazolam and 1-hydroxymidazolam, its active metabolite. Björkman (pp. 691–704) also studied midazolam and theophylline as model drugs to explore the predicted pharmacokinetic disposition values compared with real values, using physiological data for neonates and children up to 15 years old, gleaned from the literature. Importantly, a reference source of physiological data could be compiled and validated in this study for a variety of organ and tissue weights, organ blood flows, and body spaces.

The allometric scaling technique based on body weight or body surface area often fails to predict drug dosages, especially in neonates and infants [10], but Knibbe and colleagues (pp. 705–11) successfully demonstrated the relation between pharmacokinetic parameters in rats, children, and adults for propofol, using the allometric equation. The values estimated were in good agreement with literature data for clearance and volume parameters.

These rapidly evolving methods need further development, but are taking both the thinking and the practice of paediatric dose estimation from what Lew Sheiner aptly termed the 'exploratory' to the 'confirmatory' step [11].

In his paper 'How children's responses to drugs differ from those of adults' Stephenson (pp. 670–3) argues that in general children's responses to drugs have a common receptor, cellular, and general physiological basis to adults, irrespective of age or stage of development, and

that we should look carefully for dynamic surrogate endpoints to use in designing studies in children. He warns about cases of true age-dependent differences (for example warfarin and ciclosporin) and discusses the concept of programming, which is the production of a permanent effect resulting from a stimulus applied at a critical and sensitive point in development, often *in utero* or during the neonatal period.

Adult clinical pharmacologists do not perhaps pay enough attention to children's requirements for palatable and accurately defined formulations. Nunn and Williams (pp. 674–6) review the current situation and point out the barriers of expense and methodological development for manufacturers and how the incoming EU regulations and incentives may bring improvements.

The administration of inaccurately measured doses to children of different ages, coupled with the uncomfortable knowledge that the majority of medicines are used 'off label' or are unlicensed for children [12], has spawned an increasing number of papers on adverse drug reactions in children, and a re-analysis of ways in which adverse drug reactions (ADRs) can be collected by regulatory authorities. The UK 'Yellow Card Scheme', recorded from the year 2000, contains 43 000 reports for children [13]. The MHRA has estimated that about 8% of Yellow Card Reports in 1997–98 were for those aged under 18 years of age [14]. The EU strategy for paediatric medicines regulation will be considering a European-wide pharmacovigilance database.

Three papers from the University of Aberdeen (pp. 677–83, 712–17, 743–9) report on monitoring ADRs from pharmacies and primary care. In the pharmacy based prospective pilot study, the parents or guardians of children under the age of 12 who received a prescription for amoxicillin, salbutamol, paracetamol, or ibuprofen suspension, or for whom an over-the-counter purchase of paracetamol or ibuprofen suspension was made, were asked to report ADRs over five days. The results suggested that this method of ADR reporting was feasible but, like other methods, suffered from the problem that initial high uptake waned with time, resulting in overall under-reporting. The second study was based on two large primary-care data sets (the General Practice Research Data Base) and the continuous morbidity monitoring subset of the General Practice Administration System of Scotland. Asthma was chosen as a common disease for consultations, and in the study of 214 medicines in children aged between 0 and 16 years it identified no unlicensed medicines (which is some consolation), but significant 'off-label' prescribing, especially in younger children. Both lower and higher doses than are recommended in the SPC were reported, again

reflecting the need for optimal dose-ranging studies in children. Novak *et al.* (pp. 712–17) report on a primary-care study in children taking long-term antiepileptic therapy, in which they found that 3% of children had coprescribed medicines that could have given rise to serious drug–drug interactions, raising the question of attention given to information in the SPC and Patient Information Leaflets. Similarly disturbing ADR reporting is presented by Titchen *et al.* from Australia (pp. 718–23), regarding the use of nonsteroidal anti-inflammatory drugs (including COX-2 Inhibitors) and paracetamol in a paediatric hospital. There were 19 reports of ADRs over 5 years, predominantly rash and gastrointestinal and respiratory effects; 36% were deemed preventable.

At a time when there is a call for more and better medicines for children, it may seem perverse to scrutinize prospectively the efficacy and safety of older medicines, which may have been in use for many years, in order to question their continued use in children. But in the era of evidence-based medicine, paediatric therapeutics should not be excluded. Pritchard *et al.* (pp. 725–9) report that in a systematic review of (only) 4 randomized control trials that met a reasonable standard, there was no robust evidence of efficacy for the treatment of gastro-oesophageal reflux and gastro-oesophageal reflux disease in children. Grieve *et al.* (pp. 730–5) identified 79 chemical entities that had been granted a patent extension through the FDA's Paediatric Exclusivity Provision. Via a questionnaire, a panel of seven paediatric consultants in New Zealand and Australia were asked to assess the importance of the 79 medicines granted extensions, by (a) usefulness (b) the number of patients likely to be treated in each age group, and (c) existing acceptable alternative medicines. The results were compared in the UK, the USA, Australia, and New Zealand. Perhaps not surprisingly, in each country licensing was influenced by perceived usefulness and the number of patients that could be treated; these measurable improvements were greater among older children. As the authors point out, these findings may be the result of market incentives and greater ease of conducting trials in older age groups. In a companion paper (pp. 736–42), the same group report on the number of licensed paediatric medicines in Australia between 1998 and 2002. There was no change in the proportion of medicines licensed for children in Australia in that period but a fall in the proportion of formulations suitable for young children.

We worry about the safe and effective use of paediatric medicines produced by the classical routes of drug evaluation. But there is evidence of increasing use of complementary medicines in children [15]. Ekins-Daukes and colleagues (pp. 743–9) investigated

primary-care prescribing of homeopathic medicines for a range of conditions, using computerized prescribing data from general practices in Scotland. 22% of the practices prescribed homeopathic medicines for 191(1.1/1000) registered children, and most were for children under the age of 1 year. Although this seems to have been limited to a small number of active prescribers, and for self-limiting conditions, practitioners will need to gain some knowledge in this area, especially concerning the potential of drug interactions.

The UK is fortunate in having a National Health Service from which medical databases can be constructed. GPRD, the Yellow Card Scheme, MEMO, and the IMS Health databases have long been used for extracting information on the use of medicines in adults. Their use is now increasing in paediatric research, particularly into adverse drug reactions and medication errors. Wong and Murray (pp. 750–5) provide a review of the available databases, with comments on their relative strengths and weaknesses.

The papers in this special paediatrics issue cover a wide spectrum of relevant and fascinating paediatric topics in clinical pharmacology and therapeutics. Let us hope that both paediatricians and clinical pharmacologists can learn from each other for the benefit of our children.

References

- 1 Kearns GL, Abdel-Rahmen SM et al. Developmental Pharmacology – Drug disposition, action and therapy in infants and children. *N Engl J Med* 2003; 349: 1157–67.
- 2 US Food and Drug Administration Centre for Drug Evaluation and Research. Food and Drug Administration Modernisation Act of 1997 – Section, 111. Paediatric Studies of Drugs: <http://www.fda.gov/cder/guidance/105-115.htm> 1997.
- 3 US Food and Drug Administration. Best Pharmaceuticals for Children Act. <http://www.fda.gov/opacom/laws/pharmkids/contents.html> 2002.
- 4 Regulation of the European Parliament and of the Council on Medicinal Products for Paediatric use and amending council regulation (EEC) No 1768/92, 2001/83432004 Directive /EC and Regulation (EC) No 726/2004. <http://pharmacos.eudra.org/F2/home.html>
- 5 Getting the right start: National Service Framework for Children: April 2003. <http://www.doh.gov.uk/nsf/children/gettingtherightstart>
- 6 Royal College of Paediatrics and Child Health. Safer and Better Medicines for Children – Developing the Clinical and Research Base of Paediatric Pharmacology in the United Kingdom. London: RCPCH Publications Ltd., 2003.
- 7 Call for expressions of interest to become Local Research Networks within the Medicines for Children Research Network: *BMJ Careers* 2005 23 April a3.
- 8 Royal College of Paediatrics and Child Health. Medicines for Children. London: Royal College of Paediatrics and Child Health, 2003.
- 9 CDER Paediatric Decision Tree. <http://www.fda.gov/cder/mapp/4000.4.pdf>
- 10 Johnston TN. et al. A comparison of methods to predict drug clearance in neonates, infants and children. *Brit J Clin Pharmacol* 2004; 57: 677–8.
- 11 Sheiner LB. Learning versus Confirming in Clinical Drug development. *Clin Pharmacol. Ther.* 1997; 6: 275–91.
- 12 Choonara I, Conroy S. Unlicensed and off-label Drug use in Children: Implications for Safety. *Drug Saf* 2002; 25(1): 1–5.
- 13 Clarkson A, Choonara I. Surveillance for fatal suspected adverse drug reactions in the UK. *Arch Dis Child* 2002; 87: 462–6.
- 14 Independent Steering Committee Report of an Independent Review of Access to the Yellow Card Scheme. London: the Stationery Office, 2004.
- 15 Simpson N, Roman K. Complementary medicine use in children: extent and reasons. A population-based study. *Br J Gen Pract* 2001; 51(472): 914–6.