Bitter medicine

New regulations aim to address the dearth of clinical safety trials for drugs used in children

The German philosopher Dietrich Bonhoeffer (1906–1945) once famously commented that “the test of the morality of a society is what it does for its children.” Yet, in many cases, modern care of sick children seems to fail Bonhoeffer’s test. Too often, drugs are inadequately tested for safety and efficacy specifically in children, and the relatively few paediatric studies that are performed often lack basic safeguards. There is even a deficiency of basic research to address questions as fundamental as how children react to and metabolize drugs. In response, legislators and regulatory authorities have implemented new legislation aimed at better protecting children and stimulating research into paediatric treatments.

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Obviously, parents want their children treated with the most effective, safest and thoroughly tested medicines. In practice, however, paediatricians often have to base their treatment decisions on disturbingly flimsy evidence. Between 11% (in general practice) and 72% (in intensive care) of the drugs administered to children are not approved for the condition for which they are prescribed (Hill, 2005). Furthermore, the data about a drug provided by the company that supplied the medicine does not usually contain the information that clinicians need in order to use the medicine safely in children. A review of the data supplied with 1,497 drugs between 1999 and 2001 found

that 81% of drugs used in children less than one month old, and 72% of drugs used in children 6–12 years old, contained inadequate dosing information for that age (Tan, 2003). “There is a very wide practice and knowledge gap between adults and children,” commented John Warner, Professor of Paediatrics and Director of Research for the Women and Children’s Clinical Programme Group at Imperial College, London, UK. “Most pharmacological and clinical research is performed on adults and slowly diffuses down to children. There’s been a failure at all levels—funding bodies, pharmaceutical companies and paediatricians themselves—to perform pharmaceutical research in children.”

Historically, this failure has led to children suffering unnecessarily, noted Helen Sammons, Associate Professor in Child Health at Derbyshire Children’s Hospital in the UK. In the late 1950s, clinicians realized that treating newborn babies with high intravenous doses of the antibiotic chloramphenicol triggered a distressing grey tinge. The babies’ body temperature dropped and some suffered from heart and circulation problems, as well as severe vomiting (Weiss *et al*, 1960). In the 1990s, children undergoing intensive care were sedated with high doses of the intravenous anaesthetic propofol, which seemed to trigger metabolic acidosis and myocardial failure (Bray, 1998). “Too often we have to base practice on case reports or small observational studies, rather than randomised controlled trials with sufficient patients to be statistically rigorous,” Sammons commented. “If we had performed the studies, these reactions probably would have emerged sooner.”

Between November 1997 and December 2000 the US Food and Drug Administration (FDA; Rockville, MD, USA) received 7,111

adverse event reports concerning children younger than two years of age; 11% proved fatal, with 84% of the deaths occurring during the first year of life. Overall, 61% of adverse events were severe and resulted in, for example, death, disability, congenital abnormality or hospitalization. In 25% of cases, the mother exposed the child to drugs during pregnancy, delivery or through breastfeeding (Moore *et al*, 2002). “These figures clearly demonstrate that pharmaceutical companies have the moral obligation to test drugs to avoid side effects in children,” commented Domenico Franco Merlo from the Department of Epidemiology and Prevention at the National Institute for Cancer Research in Genoa, Italy.

Of course, other factors contribute to the paucity of paediatric studies. Ethical concerns, in particular the granting of informed consent, are an obvious problem for conducting clinical research on children. Informed consent requires that the patient understands the potential risks and benefits, and agrees to participate in the study without coercion. In principle, children can agree or disagree to participate in a study, but clinicians can only obtain their ‘consent’ if the child has reached a level of intellectual and emotional maturity that allows it to make an informed decision. In lieu of this, researchers obtain informed consent from parents or legal guardians. Nevertheless, the fundamental ethical principles governing research using children were defined almost 20 years ago by the United Nations’ Convention on the Rights of the Child (UN, 1989): “So, ethics cannot be the reason for the limited paediatric drug testing,” Merlo commented.

Commercial factors—rather than ethical concerns—seem to be the most likely explanation for the dearth of paediatric

trials. Such studies tend to be very expensive, and the relatively small market for medicines in children means that the commercial returns for a drug company usually do not warrant the investment. "Pharmaceutical companies can calculate easily whether it is cost-effective to perform a study in any particular patient group," Warner noted. "They also know that if a drug is effective in adults, paediatric practice will evolve and clinicians will gradually start using the drug in children. The use creeps in to practice without the company performing a single study."

Against this background, regulators worldwide have attempted to kick-start paediatric research by targeting drug companies with both sanctions and rewards. The FDA, for example, can request studies to be conducted in children, and can offer extended patent protection and marketing exclusivity in return—which could translate into millions of dollars in extra sales. By March 2008, the FDA had granted exclusivity for 150 drugs and requested 842 studies enrolling more

than 49,000 children—most of which are new indications of existing drugs. "The large number of exclusivity agreements and study requests shows that economics and not ethics played a major role in the lack of paediatric studies," Merlo commented.

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One result of the increase in clinical studies will be more accurate dosing of drugs for children and more palatable medicines. Companies will need to develop a formulation appropriate for the age of the children enrolled in the clinical trial; at present, physicians often have to make do with adult formulations. "Often, compliance is a real problem with paediatric medicines," Sammons noted. "Medicines can have a very bitter taste, which means that the child

refuses to take the drug, or we have to measure out a tiny amount, which makes dosing mistakes more likely."

The studies also need to enrol a relatively large number of patients across a broad age range to evaluate changes in safety and efficacy as children mature—which also increases costs. The pharmacokinetics and pharmacodynamics can vary markedly between a neonate and an adolescent or adult. A study of 45 medicines found that drugs used in premature and full-term neonates tend to have half-lives that are between three- and nine-times longer when the same drug is used in adults. The half-lives of drugs in adolescents were generally similar to, or shorter than, those in adults (Ginsberg *et al*, 2002).

The pressing need to improve the quantity and quality of paediatric clinical studies has promoted a spate of new regulations in Europe. In January 2007, the European Union introduced new legislation for the development and authorization

of medicines for use in children aged 0–17 years. Starting in July 2008, companies that want to market a new medicine must, in most cases, include results from paediatric studies in their application for approval, and develop age-appropriate formulations. The European Medicines Agency (EMA; London, UK) can waive this requirement if, for example, a condition occurs only in adults—such as Alzheimer disease, age-related macular degeneration or certain cancers. In other cases, the EMA might consider it prudent to defer paediatric studies until sufficient data has accumulated in adults—although the requirement to perform trials in children remains. After approval, a drug supported by paediatric studies receives an extra six months of patent protection. From 2009, the rules will also apply to new indications, formulations and routes of administration.

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“There is now a legal obligation on pharmaceutical companies to provide paediatric studies,” commented Agnes Saint Raymond, Head of the Scientific Advice and Orphan Drugs Sector at the EMA, who leads the implementation of the Paediatric Regulation. “Unless the company obtains a waiver, if they don’t perform the paediatric study, they won’t get approval for the adult indication. However, more fundamentally, we aim to foster a complete change in the mindset towards clinical trials in children.”

To facilitate this change, the EMA launched a confederation to coordinate research across national and European paediatric research networks and centres. Meanwhile, the agency is conducting a survey of EU member states to compile an inventory of the studies needed. EU-funded studies could help to address these needs, especially if the drugs are no longer under patent protection. The EMA will also mandate long-term pharmacovigilance studies in children—an area of growing importance in drug development generally (Greener, 2008).

Meanwhile, the EU clinical trials database (EudraCT; <http://eudract.emea.europa.eu>) collects the results of paediatric clinical trials performed inside and outside the EU,

and the EMA is exchanging information on paediatric clinical studies with the FDA. “It’s too soon to see the difference that the new legislation has made,” Saint Raymond said. “We are still in the process of implementing the legislation. But EudraCT already includes 27 studies performed outside the EU, which is information that wasn’t available before.”

The EMA and the European Commission also made several ethical recommendations to better harmonize clinical research across the EU. However, harmonization could take several years. In the meantime, Merlo suggested focusing on practical steps to strengthen the ethical foundations of clinical studies performed in children, such as ensuring that ethics committees can call on paediatric expertise. Alternatively, specialist paediatric ethics committees could oversee studies in children. In addition, researchers also need to provide information appropriate for parents and children. “Even if patients are too young to understand complex research issues, they will participate only if they do not object,” Merlo remarked. “Therefore, researchers need to develop and correctly use tools specific for adults and children. For example, two information sheets might be required: one for the child, and one for the parents or guardian.”

The increased scrutiny by the EMA and local ethics committees should help to avoid some of the more methodological weaknesses that have historically undermined paediatric research. Sammons and colleagues, for example, analysed 739 paediatric trials—excluding HIV and oncology—performed between 1996 and 2002. Although moderate or severe adverse drug reactions emerged in 11% of the studies, only 2% of the papers reported using independent committees to monitor safety (Sammons *et al*, 2008), which is a widespread practice in adult clinical trials. “We were surprised that so few papers reported using an independent safety monitoring committee,” Sammons said. “We would expect that if there was a safety monitoring committee, the paper would have mentioned the fact. Researchers

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and ethics committees should never agree to participate in a paediatric study that does not include a safety monitoring committee.”

In the future, Saint Raymond expects that safety monitoring committees will oversee most paediatric studies approved by the EMA. “A drug and safety monitoring board should be part of the basic approach for paediatric studies,” she said. “Many pharmaceutical companies monitor safety to a high standard. However, some do not. So the sponsor will need to explain why a study doesn’t have a drug and safety monitoring board.”

The legislative and regulatory changes should encourage applied research, but researchers also need to address some fundamental questions. “We don’t know much about basic pharmacokinetics in children,” Saint Raymond commented. “We don’t really understand why children and adults develop different patterns of side effects to many common drugs, or how to prevent toxic effects, such as impaired growth. In particular, we have very little understanding of the effect of drugs on the developing brain. We don’t have any agreed end points and there are very few animal models that allow us to assess, for example, the effect of anti-epileptic drugs on the growing brain.” She expects that the paediatric committee will mandate studies to examine these issues.

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Warner calls for more research into diseases in early life. “We look at a disease in adults and then move to children,” he said. “But that’s often the wrong way around. Many diseases have roots in childhood or even in the womb.” For example, the *in utero* environment can influence the risk of developing cardiovascular disease, allergic conditions, some cancers, and serious psychiatric diseases, such as schizophrenia, in later life—so-called fetal programming. “There is accumulating evidence that interventions early in life can improve long-term outcomes. So investigating the early origins of disease has enormous potential to prevent conditions that

need treatment in adults," Warner added. "However, it is often very difficult to get funding for these studies." Nevertheless, some projects are underway. NewGeneris, for example, is a large study conducted within the EU's 7th Framework Programme to investigate whether prenatal and early-life exposure to genotoxic chemicals in food and the environment contribute to childhood cancer and immune disorders (www.newgeneris.org).

Only time will tell if the new legislation is enough to ensure the safety of children and kick-start paediatric research. However, it will be many years before the evidence base is as robust as that in adults. In the meantime, paediatricians will continue to treat children based on inadequate information. Ironically, the lack of evidence often leads to a situation that many parents want to avoid when they refuse consent for their child to take part in a study. "Some parents worry that their child will be a guinea pig in a clinical study," Warner concluded. "But the use of inadequately tested paediatric drugs means that children are often guinea pigs in clinical practice."

REFERENCES

- Bray RJ (1998) Propofol infusion syndrome in children. *Paediatr Anaesth* **8**: 491–499
- Ginsberg G, Hattis D, Sonawane B, Russ A, Banati P, Kozlak M, Smolenski S, Goble R (2002) Evaluation of child/adult pharmacokinetic differences from a database derived from the therapeutic drug literature. *Toxicol Sci* **66**: 185–200
- Greener M (2008) First do no harm. Improving drug safety through legislation and independent research. *EMBO Rep* **9**: 221–224
- Hill P (2005) Off licence and off label prescribing in children: litigation fears for physicians. *Arch Dis Child* **90** (Suppl 1): 17–18
- Moore TJ, Weiss SR, Kaplan S, Blaisdell CJ (2002) Reported adverse drug events in infants and children under 2 years of age. *Pediatrics* **110**: e53
- Sammons HM, Gray C, Hudson H, Cherrill J, Choonara I (2008) Safety in paediatric clinical trials—a 7-year review. *Acta Paediatr* **97**: 474–477
- Tan E, Cranswick NE, Rayner CR, Chapman CB (2003) Dosing information for paediatric patients: are they really "therapeutic orphans"? *Med J Aust* **179**: 195–198
- UN (1989) *Convention on the Rights of the Child*. Geneva, Switzerland: Office of the United Nations High Commissioner for Human Rights
- Weiss CF, Glazko AJ, Weston JK (1960) Chloramphenicol in the newborn infant. A physiological explanation of its toxicity when given in excessive doses. *N Engl J Med* **262**: 787–794

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