

## The trials and tribulations of doing drug research in children

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In the current era of evidence-based medicine, physicians caring for children struggle to define a standard of care with drugs that have not been evaluated in children. Because medications are less commonly tested in children, much of pediatric prescribing involves educated guesses about doses, safety and effectiveness.<sup>1</sup> A lack of appreciation of the differences between children and adults often results in the inappropriate extrapolation of data derived from adults to the pediatric population. This situation is dangerous. It either deprives children of the benefits of drug therapy withheld because of lack of information or exposes them to unknown side effects. In fact, adverse reactions to medication are a significant cause of death and injury in infants and children under 2 years of age.<sup>2</sup> We need additional drug testing in the pediatric population.

It is commonly perceived that drug use in children is infrequent and confined to a small number of drug classes, primarily antimicrobials, and that there is little financial incentive for industry to conduct major clinical trials of drug therapy in children. However, recent data indicate that increasing numbers of children in the United States are taking prescription medications.<sup>3</sup> As well, a study of private drug plan databases representing roughly 30% of Canadian children younger than 18 years showed a claim for a prescription drug recorded for approximately half the children during a 12-month period (1999–2000).<sup>4</sup> Ensuring the availability of evidence-based information on the efficacy, dosing and safety of medications commonly used in children not only is ethically appropriate but also seems a worthwhile economic investment for industry as well as children's hospital foundations, the Canadian Institutes of Health Research (CIHR) and other funding agencies.

Practical difficulties particular to drug studies partially explain why such research in children has lagged behind that in adults. The most common hindrances cited are ethical, technical and logistic. In a recent survey of pediatricians in Canada, we found that most (78%) perceived drug research in children to be more difficult to perform than other medical research; the main barrier identified was ethical considerations.<sup>4</sup> Children are generally viewed by the medical research community as a vulnerable group that needs protection from the potential harm of participating in a drug study. However, it can be argued that it is unethical to subject pediatric patients in clinical practice to the risks of therapy with medications that have not been adequately evaluated in their age group.

Technical difficulties, including the need for frequent

blood sampling and the inability to measure endpoints such as pain and quality of life in very young children, have been cited as an impediment to testing drugs in children. However, advances in clinical pharmacology such as population pharmacokinetics and sparse sampling (testing only a couple of samples from each child in a large group), along with increasing expertise in clinical epidemiology and outcomes research, are reducing these concerns. Improved tools for assessing pain and measuring quality of life are now available for use in younger groups.

Logistically, pediatric trials are often difficult to perform. For many pediatric diseases, such as infantile spasms and juvenile rheumatoid arthritis, a relatively small number of children are affected, so there are recruitment problems. With increasing collaboration between researchers, the potential for multicentre trials will improve and facilitate the study of drug therapy, as has happened in pediatric oncology. For example, the Pediatric Pharmacology Research Unit (PPRU) Network in the United States, with its stable infrastructure of study sites and trained, experienced personnel, has enhanced the ability to conduct well-designed and adequately powered pediatric drug trials.<sup>5</sup>

Adding to these practical barriers and the perceived lack of financial incentive to conduct drug research in the pediatric population, the drug-approval process in Canada has historically not included an absolute requirement for studies in children. Recent policy innovations in the United States have been a step forward in encouraging the testing of medications in children. The US Food and Drug Administration (FDA) Modernization Act of 1997 allowed manufacturers who voluntarily conducted studies of drugs in children to obtain an additional 6 months of marketing exclusivity.<sup>6</sup> An FDA status report to the US Congress in January 2001 stated that the pediatric-exclusivity provision had done more to generate clinical studies and useful prescribing information for the pediatric population than any other regulatory or legislative process to date.<sup>7</sup> The "Pediatric Rule" allowed the FDA to require studies for certain products in children;<sup>8</sup> however, the FDA is barred from enforcing this requirement, the US District Court for the District of Columbia having ruled that the FDA did not have the authority to issue the regulation.<sup>9</sup> The Best Pharmaceuticals for Children Act,<sup>10</sup> passed in 2002, reauthorized the 6 months of marketing exclusivity for pediatric drugs. It appears that the United States has taken the lead; the rest of the world should learn from these experiences.<sup>11</sup>

Although similar policy efforts have not yet occurred in

Canada, all is not silent here. There is considerable expertise in this country in pediatric clinical pharmacology, clinical trials, outcomes research and bioethics. One attempt to capitalize on this expertise is the Canadian Paediatric Clinical Pharmacology Network. Over the past 2 years, members of the 6 academic centres in the network have identified key challenges and have been developing strategies to address them. There are only pockets of pediatric drug research in Canada. However, if stable funding were available, as in the United States, a robust and collaborative made-in-Canada effort could be mounted to address the key research questions in pediatric drug therapy and attempt to overcome some of the barriers to research. In the meantime, we need to take advantage of existing expertise, such as specialty-area and disease-specific networks, to provide an established framework for multicentre clinical drug trials.

Now is an opportune time to encourage drug research in children in Canada. The success of the US model holds several important lessons, and similar initiatives might increase our capacity for drug research in Canada. New drugs continue to enter the market in increasing numbers, and we must be proactive rather than reactive. There is a need for organizations with a key interest in pediatric therapeutics, such as Health Canada, the Canadian Paediatric Society and the CIHR, to develop clear guidelines on the ethical conduct of drug trials in children and to revise existing guidelines (such as the Tri-Council guidelines<sup>12</sup>) to incorporate more information relevant to pediatric subjects. Pediatricians and other physicians need to lobby government and industry for increased investment in drug studies in Canadian children. Despite the difficulties, we must accept the challenge and move pediatric therapeutics forward, providing physicians with the evidence-based information required for effective and safe treatment.

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