EDITORIAL

Why are children still therapeutic orphans?

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One of the paradoxes of drug regulation is that children have ended up being denied the protections afforded by the very laws which were introduced to ensure the efficacy and safety of drugs following disasters such as the thalidomide tragedy. Children have become therapeutic orphans[1] because they are either denied the use of many new medications or exposed to medications that have bypassed rigorous evaluation. Many marketed drugs that are commonly used, or could potentially be used in children, have not been studied in the relevant age groups[2] and so are not approved by regulatory authorities for use in children.

Information about the safety and efficacy of medications in the youngest, and most vulnerable, paediatric age groups is especially scarce.[2] Any prescription of drugs outside the specifications of the product licence (such as for a different age, dose, route or indication) is 'off-label' use.[3] Some medicines that are given to children are not registered by the Therapeutic Goods Administration for any indication in adults or children ('unlicensed' use).

This paradox poses significant clinical, ethical and legal dilemmas for prescribers.[4] It is difficult to practise evidence-based medicine when there is little (or no) evidence. Yet, clinicians tend to choose to prescribe a new drug despite a lack of paediatric data rather than deprive children of a potentially beneficial therapy. The practice is widespread; between 40 and 90% of paediatric prescribing is for off-label use or for unlicensed drugs.[3,5] Although unlicensed or off-label prescribing is not illegal, and in some cases may be entirely appropriate, it does bypass the safeguards of the drug regulatory process and places a greater onus of responsibility on the individual prescriber. The validity of 'informed consent' to therapy based on little or no information also raises ethical concerns.[4]

While unlicensed or off-label prescribing may be acceptable as an exception, it is clearly unacceptable when it becomes the rule. Children are disadvantaged in many ways by this situation.

First, extrapolating the results of adult studies means that children may be exposed to ineffective therapies (or to ineffective doses of potentially effective therapies) and to unknown risks of adverse effects. There are many biological differences between adults and children of different ages which mean that the evidence of effectiveness and safety in adult studies is not generally applicable to children (for example chloramphenicol and the grey baby syndrome).

While it may be tempting to give the benefit of the doubt to new drugs that have not been studied in children, this may place more children at risk than if the drug was used as part of a controlled trial.[6] Adverse effects are more common when drugs are used off-label[7] and some children have died as a result.[8] Ironically, this information is also hard to come by since spontaneous reporting of adverse drug reactions as part of standard post-marketing surveillance may be less likely with off-label prescribing.[2,4]

Second, the lack of information about new drugs means that children may be unable to benefit from therapeutic advances that are available to adults.

Third, even if a drug has good evidence of paediatric efficacy and safety, it may be unavailable in formulations (for example liquids) that are suitable for children.

In this issue...

The proverb 'You are what you eat' is relevant for medical practice. Lynne Daniels tells us that patients are likely to make a better recovery from surgery if they are well nourished, while John Wark and Caryl Nowson remind us of the importance of an adequate calcium intake.

The origins of the proverb are uncertain. Perhaps it came from China, where herbs have been used as medicines for centuries. George Li, Colin Duke and Basil Roufogalis discuss the quality of traditional Chinese medicines, and John McEwen and Fiona Cumming explain how these products are regulated by the Therapeutic Goods Administration.

Eight new drugs have been marketed in Australia since the previous issue of *Australian Prescriber*. How many of these new drugs will make the top ten? As usual, this year's top ten features several drugs which are used to treat conditions associated with an unhealthy lifestyle, including a poor diet.

Fourth, evidence from well-conducted studies in children may not always be reflected in the product information, if it becomes available after marketing of a new drug. This results in the contradictory and confusing situation (for the prescriber and consumer) where prescribing is evidence-based yet not consistent with the product information, which may state 'Not approved for use in children'. As Consumer Medicine Information leaflets are based on the product information, children and parents are further disadvantaged by not having access to appropriate drug information.

Fifth, the current system also means that children are denied equitable access to subsidised medication. The Pharmaceutical Benefits Scheme does not include off-label prescribing.

Finally, uncritical acceptance of widespread off-label drug use by prescribers additionally disadvantages children by removing the incentive for the pharmaceutical industry to properly evaluate drugs for paediatric use.

The pharmaceutical industry has been reluctant to conduct drug studies in children, mainly because of the low profitability and perceived greater risks of paediatric drug research. Many of the other obstacles to drug research in children have been largely overcome by recent advances in research methods and development of collaborative approaches between investigators.[9,10] Drug studies that are scientifically valid, feasible and ethical are now possible and 'there is a moral imperative to formally study drugs in children so that they can enjoy equal access to existing as well as new therapeutic agents'.[6] The Food and Drug Administration in the USA now requires manufacturers of new and marketed drugs to conduct paediatric studies and in some circumstances will provide financial incentives for this research.[9] Similar changes are currently being proposed by the European Union.[11]

The policy changes in the USA have vastly increased the number of drug studies in children and expanded the evidence base for paediatric therapeutics. However, it is evident that these initiatives have favoured the study of more profitable drugs. Drugs lacking patent protection (for example most older antibiotics) and those with a small market still remain unstudied.[12] Public funding is therefore being made available in the USA specifically for the study of off-patent drugs used in children. This initiative should go a long way towards remedying the woeful state of the evidence base for paediatric therapeutics. Australian children will no doubt benefit greatly from these global initiatives, but much more work needs to be done before they enjoy truly equitable access to useful medicines.

Developing successful solutions for this age-old problem requires new ways of thinking and action by all concerned. Clinicians should work with researchers to ensure that the study of medicines likely to deliver the greatest health benefit to children receives the highest priority. Drug companies should be encouraged to conduct more high quality research on drugs that may be used in children and to ensure that available research is incorporated into the product information. They should be encouraged to ensure children's continued access to new and old drugs in suitable formulations, even if this may not be very profitable. Withdrawal of useful medications should be strongly discouraged, unless there are safety concerns or clearly superior alternatives are available.[13] Clinicians, researchers, policy makers and consumers should work together with the pharmaceutical industry to develop innovative ways of achieving these goals as a matter of urgency.

We have allowed children to remain therapeutic orphans for far too long. Clear and feasible solutions now exist to remedy this problem. It is time that we stopped discriminating against our children and high time that we finally gave them their rights to the benefits of full therapeutic 'citizenship'. They deserve nothing less and nothing less will do!

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