CURRENT TOPIC

Medicines for children—the last century and the next

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Paediatricians, neonatal/paediatric pharmacists, and chief executives of hospital trusts recently received a position statement on the use of unlicensed medicines, produced by the Joint Standing Committee on Medicines of the Royal College of Paediatrics and Child Health (RCPCH) and the Neonatal and Paediatric Pharmacy Group (NPPG).

The licensing of medicines

Before a pharmaceutical company can promote a drug, it must obtain a licence.[1] Following the 1960s thalidomide disaster,[2] "legislation was introduced to ensure that no new drug could be marketed until independent experts were agreed that it had been adequately tested and was safe".[2] The process differs between countries but the principles are that the company must show the safety, quality, and efficacy of the drug when given in the dose and for the disease and age group recommended in the Summary of Product Characteristics (SPC). Drugs are increasingly licensed on a European Union wide basis. In the UK, doctors can legally prescribe drugs without a licence (unlicensed, UL) or outside the terms of the licence (off label (OL)—for example, in a different dose, as a different formulation, or for a different disease or age group). Prescribing outside the licence is relatively common for hospitalised children.[3–6] In a neonatal intensive care unit 90% of infants receive UL or OL drugs. In primary care, 11–33% of prescriptions for children are UL/OL.[7 8]

As paediatricians can still prescribe, is this a problem?

The current licensing arrangements ensure a rigorous assessment of most drugs used for adults. When a medicine is prescribed OL/UL, these safeguards are absent, extrapolation from adult data is necessary (despite the great biological differences between adults and children[9 10] and between children of different ages[11]), and children may be given inadequate doses or exposed to unknown risks. There is also evidence which suggests that adverse drug reactions (ADRs) are more likely with UL/OL medicines.[12] Furthermore, standardised post-marketing surveillance will not occur, spontaneous reporting of ADRs may be less common, and the patient information leaflet (PIL) will confuse the parents if it states "not to be used in children".

How do letters to chief executives of NHS Trusts help?

POSITION STATEMENT ON THE USE OF UNLICENSED MEDICINES

This explains the anomalous position of drugs used for children (about which hospital managers, lawyers, and therapeutics committees may be unaware) and states the following principles:

- Those who prescribe for a child should choose the medicine which offers the best prospect of benefit for that child, with due regard to cost
- The informed use of some unlicensed medicines or licensed medicines for unlicensed applications is necessary in paediatric practice
- Health professionals should have ready access to sound information on any medicine they prescribe, dispense, or administer, and its availability
- In general, it is not necessary to take additional steps, beyond those taken when prescribing licensed medicines, to obtain the consent of parents, carers, and child patients to prescribe or administer unlicensed medicines or licensed medicines for unlicensed applications
- NHS Trusts and health authorities should support therapeutic practices that are advocated by a respectable, responsible body of professional opinion.

In the absence of data from randomised trials, the Health Technology Assessment Committee and the Quality of Practice Committee of the RCPCH recommend consensus methods.[13] Consensus from the British Isles was used to produce the book *Medicines for children*.[14 15] The status of *Medicines for children* as the current best authority on OL/UL prescribing for children may assist paediatricians in persuading hospitals to purchase copies. In the UK, the importance of peer concurrence can be traced to the Bolam judgment of 1957: "A doctor is not guilty of negligence if he has acted in accordance with a practice accepted as proper by a responsible body of medical men skilled in that particular art".[16]

PATIENT INFORMATION LEAFLETS

Currently, manufacturers' PILs are enclosed with medicines. However, European law dictates that these must concur with the information in the SPC. Therefore, if the drug is not licensed for children the PIL will state this,

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even if the drug is widely used in paediatric practice. To help communication with parents and children, and to try and avoid misunderstandings and complaints, the RCPCH/NPPG Committee on Medicines has produced a generic PIL for parents and a modified version for older children. These can be included with all paediatric prescriptions and clarify the current position. The advice of consumer groups has been incorporated and the text has a reading age of 13 years as recommended for public information documents.[17]

What else has been done?

The first step has been to increase awareness of the problems of prescribing for children and the disadvantage children may suffer.[4 9 10 18] For the first time since the 1960s, the UK Committee on Safety of Medicines has a paediatric working group, and the Medicines Control Agency is developing a paediatric strategy which considers children at every step of the regulatory process and is looking at ways of enhancing pharmacovigilance in children. The Medicines Control Agency and NHS have jointly funded a pilot assessment of a Paediatric Regional Monitoring Centre in the Trent Region. The first two training posts in paediatric clinical pharmacology have been established in the UK. There is a British Forum for the Use of Medicines in Childhood which is promoting the concept of a network of centres for drug research, as in the USA.

In Europe, more data for children have been requested from pharmaceutical companies but this "softly, softly" approach has had little impact to date.[19] Of 45 new substances licensed in 1995–98, 29 were of possible use in children but only 10 were licensed for paediatric use. The French Presidency of the European Union (EU) considered paediatric medicines a high priority and in December 2000 the EU Council invited the European Commission to suggest "incentives, regulatory measures or other supporting measures in respect of clinical research and development to ensure that new medicinal products for children and medicinal products already on the market, are fully adapted to the specific needs of that population group."

In the USA, the Clinton administration legislated so that companies who perform paediatric studies on drugs which may be appropriate for children can be rewarded with a six month extension to the exclusive patent.[20] Unfortunately, this simplistic approach may encourage multiple paediatric studies of "me too" drugs of undoubted benefit to children as a drug class (for example, beta blockers for hypertension) but not necessarily justifying trials of every drug in that class.

What still needs to be done?

The major obstacle remains the dearth of good data in children on the pharmacokinetics ("what the child does to the drug"), pharmacodynamics ("what the drug does to the child"), and safety of many drugs. There are plausible financial reasons why the pharmaceutical industry is more reluctant to study drugs in children: the market may be smaller (for example, children with hypertension) and the doses are smaller so they may not recoup their research costs. Where the market is large (for example, antibiotics) or the disease severity allows a high unit price (for example, surfactants), companies do study drugs in children and successfully apply for licences, suggesting that industry can overcome perceived ethical problems[21 22] and litigation risks.[23 24]

The RCPCH statement on research ethics clarifies that children can participate in studies not of direct benefit to themselves[25] and the RCPCH/NPPG Medicines Committee has lobbied the EU to adopt this position. Our concerns were addressed by the European Parliament in December 2000:

> Normally, these persons (individuals incapable of giving consent, such as minors) should only be included in clinical trials when there are grounds for expecting that the administering of the medicinal product would be of direct benefit to the patient ... However, there is a need for clinical trials involving children to improve the treatment available to them. Children represent a vulnerable population with developmental, physiological, and psychological differences from adults, which make age and development related research important for their benefit.[26]

The Griffiths Report stated that research involving children should be subject to an even greater degree of supervision than research in general,[27] leading to the possibility that there will be discrimination against children's research in comparison with adults.[28] There is some evidence that children enrolled into trials have better outcomes, irrespective of which arm of the trial they are randomised to,[22] and many paediatricians would argue that it is unethical not to undertake drug trials in children. It is not acceptable that children require medicines which have not been properly tested.[15 26] On the other hand, commercially funded trials may not all be ethically valid. Of 136 randomised trials of myeloma in adults, 74% of commercially funded trials favoured the tested treatment over control treatment whereas 53% of trials funded by government or non-profit organisations favoured the new treatment.[29] In perfect equipoise (complete uncertainty),[22 30] half of all trials should favour the new treatment and half the controls.

Historically, there may have been a lack of advocacy for children's research because initially this was not a high priority for a young specialty, and until recently the Royal College of Physicians represented (or did not?) the needs of children on many government bodies. Funding may be difficult because of smaller numbers (for example, children with cancer) or smaller peceived public health impact (for example, children with hypertension). Both advocacy for children and paediatric academic research remain vulnerable.[28 31] However, more drug research could be conducted within the NHS.[32] "Culyer money", earmarked for research, may represent 3% of an NHS hospital's

budget but it may be difficult to pinpoint the use of this money. Comparison of synthetic and natural surfactants is a good example of a pragmatic trial carried out by paediatricians in several hospitals already using and paying for these drugs,[33] albeit six years after pumactant was first granted a licence. However, if the documentation, quality control, and monitoring required of a trial within the NHS is the standard demanded of a pharmaceutical company's,[27] (and why should there be a difference?) then this may deter NHS research. The monitoring staff paid for by the pharmaceutical industry add considerable amounts to the cost of running a drug trial. I admire the quality of their data collection and envy their mechanisms for double checking. However, few in the universities or NHS have these resources or the profit generation to recoup them.

The responsibilities of paediatricians

New legislation will not solve all these problems. Efficacy for licensing is a demonstration that the drug is superior to placebo or other drugs. A combined assessment of efficacy, safety, cost, and feasibility within the NHS is the role of the National Institute of Clinical Excellence. When research in children exists, paediatricians do not always follow this and this may be addressed not by new legislation but by clinical governance[34] (Commission for Health Improvement, RCPCH, audit, local guidelines, and therapeutic committees). When large ethical trials are funded, paediatricians do not always take part to the same degree.[35] In the current trial of high frequency oscillation, the percentage of eligible babies recruited varies from 27% to 86% between participating centres. No man is an island and paediatricians cannot have it both ways; "I know best" (that is, I will not follow research based guidelines) and "we know best" (the unit as a whole will not participate in a trial which the Medical Research Council sees as sufficiently worthwhile to fund[36]) will not do. These are all professional issues, not legislative issues, and a major challenge to a young college. Moreover, the training and practice of paediatricians in prescribing is within the remit of the College's Trainee and Continuing Professional Development schemes.

Finally, the RCPCH/NPPG Medicines Committee is assisting the Department of Health and Medicines Control Agency by prioritising which drug classes need most urgent research. If ring fenced funding for paediatric drug research and development is forthcoming, watch the pages of this and other journals to read the results and inform your practice.

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