Which infants should be referred to the paediatric cardiologist?

- Those with clinically suspected congenital heart disease
- Those ventilated for severe persistent hypoxaemia, particularly if extracorporeal membrane oxygenation is being considered
- Those in whom an adequate echocardiogram is not obtained by the neonatologist or where echocardiography reveals previously unsuspected CHD.

Which infants can reasonably be assessed by a trained neonatologist echocardiographer?

- The hypotensive or shocked newborn in the first few hours of life without clinical evidence of congenital heart disease
- Those requiring assessment of ductal and/or interatrial shunting
- Those with a central line to assess its position or to exclude vegetation or thrombus
- Those in whom pulmonary arterial pressure or cardiac output needs to be assessed (once CHD has been excluded by a paediatric cardiologist in infants with persistent hypoxaemia).

Conclusions

Echocardiography is an essential part of modern neonatal intensive care. Its use should not be limited to cardiologists in the diagnosis and assessment of CHD but should be extended to the routine care of critically ill neonates. As with any investigative tool, echocardiography should be used in combination with clinical acumen and not as a replacement. Paediatric cardiologists should not be worried about neonatologists learning echocardiography, rather they should encourage, support and supervise them—live video links may even help to avoid unnecessary transfer to cardiac centres of cyanotic infants without CHD. Being involved in establishing guidelines for the safe practice of neonatal echocardiography is surely better than ignoring it.

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Licensing of medicines

The Medicines Act 1968 requires that all medicines manufactured or marketed in the UK have been authorised by the licensing authority, the Medicines Control Agency. The aim of the licensing system is to ensure that medicines are examined for efficacy, safety, and quality. Pharmaceutical companies apply for a product licence for a particular drug, and in their submission they include the indication, dose, route of administration, and age group of patient for which this applies. The licensing arrangements constrain pharmaceutical companies in that they cannot promote either an unlicensed product or a licensed product for an unlicensed indication. Doctors, however, are not restricted to prescribing licensed medicines or for licensed indications.

Drug toxicity and licensing

The Medicines Act was a response to some of the major cases of drug toxicity that occurred in the late 1950s and early 1960s. Two of these resulted in significant morbidity and mortality for the developing fetus and the newborn infant: phocomelia caused by thalidomide[1 2] and the grey baby syndrome caused by chloramphenicol.[3] It is ironic that, despite drug toxicity occurring in this age group, neonates, infants, and children receive medicines that have not been through the licensing system. Many of the medicines given to children in hospitals either do not have a product license for use in children and hence are used off label (outside the terms of the product licence) or are simply not licensed at all for use in their current formulation.[4] Recent studies suggest that up to 40% of children in hospital receive "unlicensed" medicines[5] and this is of concern to children, their parents, health professionals, the regulatory authorities, and, more recently, politicians.[6]

Pharmaceutical companies have been reluctant to seek licences for use of their products in children for a variety of reasons—the practical difficulties in organising clinical trials, the lack of a major financial incentive as the paediatric market is significantly less than that for adults, concerns about drug toxicity, and inexperience in conducting clinical trials in children.[7] It is often more difficult to organise clinical trials in children than in adults; however, adequate clinical trials can be carried out in this age group[8–10] and the fear of carrying out such trials is usually far greater than the practical difficulties involved. Children may be at greater risk for certain toxic effects and this has been highlighted by the hepatotoxicity caused by sodium valproate, which resulted in the death of more than 100 patients (most of whom were children),[11] and the development of Reye's syndrome following the use of salicylates.[12]

The need to study drugs in children

Several problems have illustrated that dosing regimens derived from adult studies cannot be extrapolated to infants and children. The importance of understanding drug metabolism in relation to development is illustrated by the toxicity of thalidomide, chloramphenicol, and sodium valproate. Thalidomide itself is not teratogenic but its dicarboxylic acid metabolite is teratogenic.[13] This metabolite, however, cannot cross the placenta and the teratogenicity of thalidomide is because of formation of the toxic metabolite by the fetus itself. An understanding of fetal metabolism is important in relation to both understanding and hopefully preventing further cases of teratogenicity. The initial dosage regimen for chloramphenicol was based on studies in adults; however, the

metabolism of chloramphenicol is impaired in neonates and therefore significantly lower doses are required to prevent toxicity.[14] Drug toxicity is not restricted to the fetus and the newborn infant; sodium valproate hepatotoxicity is thought to be related to enhanced omega oxidation.[15] This pathway is enhanced by polypharmacy and certain metabolic diseases, it also appears to be enhanced in children younger than 3 years. These examples illustrate the importance of increasing our knowledge of drug metabolism in children to minimise toxicity while ensuring efficacy.

Initiatives

Medicines for adults are evaluated to ensure that they meet acceptable standards of safety, quality, and efficacy, whereas in children they are often not evaluated. This unsatisfactory situation resulted in the setting up of a joint working party between the (then) British Paediatric Association and the Association of the British Pharmaceutical Industry, and the publication of a joint report on the licensing of medicines for children in May 1996.[16] At the same time there was discussion in the Europe Community regarding the guidance on clinical investigation of medicinal products in children. After consultation involving health professionals throughout the European Community a new guidance has been issued (March 1997), which came into force in September 1997.[17] The new guidance is a major step forward because of its emphasis on the need for product testing in children. It divides medicinal products into four categories with the following recommendations:

(1) Diseases affecting children exclusively—trials of medicinal products in children may start before any adult human exposure
(2) Diseases that mainly affect children, are of particular gravity in children, or have a different natural history in children—clinical trials in children are needed at an early stage in clinical development following demonstration of safety and reasonable (phase I and II) evidence of efficacy in adults
(3) Diseases occurring in adults and children for which there is currently no treatment—as point 2
(4) Diseases occurring in adults and children for which treatment exists—clinical trials in children should usually follow completion of adult phase III trials.

This is a sensible approach that should encourage the pharmaceutical industry to concentrate on clinical trials for conditions in children where there is either no or inadequate treatment at present.

Response

The new guidance also encourages pharmaceutical companies to carry out trials in children where the product is likely to be used in children. In the past there was no pressure on the pharmaceutical company to carry out trials in children. The recent report by the House of Commons health committee on the specific health needs of children and young people confirmed that the present system was unacceptable.[6] The Royal College of Paediatrics and Child Health through its medicines committee has shown that it is keen to cooperate with both the pharmaceutical industry and the regulatory authorities. The Medicines Control Agency in the UK has played a leading role in the development of the new guidance for Europe. We hope that pharmaceutical companies respond to the challenge of ensuring that medicines used in children are evaluated scientifically.

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Epidemiology of head injury

Head injury is recognised as a major public health problem that is a frequent cause of death and disability in young people and makes considerable demands on health services. Epidemiological data are required to initiate appropriate preventive measures and to plan necessary services. However, reliable statistics are difficult to extract from routinely collected data.

International statistics for accidental deaths and road accident deaths do not identify head injuries, but they do indicate differences in accident rates between countries and over time. For example, road traffic accident (RTA) deaths are more than twice as frequent in France, Australia, and the USA as in the UK or the Netherlands, but in developed countries they are steadily decreasing each year.[1] In developing countries accident rates are increasing as traffic increases, and they greatly exceed those of developed countries. Asked about the main health hazard of the next decade a Chinese professor of public health