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Training in Paediatric Clinical Pharmacology

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Abstract

Paediatric clinical pharmacology is a relatively new discipline with training programmes established in several countries worldwide. Within the UK, there is no formal approved training programme. This is an area of increasing interest and the essentials of training are described. This includes areas similar to adult clinical pharmacology but also areas specific to paediatrics.

Key words: Clinical pharmacology – Children – Neonates

The Need

There is an increasing concern regarding the use of medicines in children. Many of these medicines have not been formally tested in clinical trials, and unlicensed and off-label drug use is widespread[1–3]. There is widespread agreement between paediatricians, clinical pharmacologists, the pharmaceutical industry and regulatory authorities, that this situation is unsatisfactory. There is support for developing training programmes in the field of paediatric clinical pharmacology from both paediatricians and clinical pharmacologists who feel that clinical pharmacology needs to expand beyond adult medicine[4]. The scientific study of medicines in children of all ages would be improved by the establishment of an agreed training programme.

Training

The background of those individuals who may wish to undergo training in this field may include individuals who have previously trained in paediatrics or clinical pharmacology. This needs to be taken into account in devising a training programme for a specific individual.

Individuals with experience in adult clinical pharmacology may decide to seek training in paediatric clinical pharmacology. These individuals will need to receive training in clinical paediatrics and also the specific aspects of paediatric clinical pharmacology listed below:

- Ethics of clinical trials in children
- Pharmacokinetic studies in children
- Analytical methods
- Ontogeny of drug metabolism
- Pharmacogenetics
- Non-invasive methods of studying drug metabolism
- Age-related delivery systems (formulations/inhalers)
- Validity of animal models for the developing human
- Age-dependent pharmacodynamic studies in children
- Neonatal clinical pharmacology
- Drug toxicity in the fetus, infant and child
- Surveillance for drug toxicity
- Regulatory requirements for the licensing of medicines for children

Ethics of Clinical Trials in Children

Previously it had been felt that clinical trials in children were not ethical. There has now been a change in attitude and it is recognised that to give children medicines that have not been tested in clinical trials is unethical. There are, however, differences between children and adults in that the use of healthy children for pharmacokinetic studies is considered inappropriate by most health professionals working in this field. There is also the question of whether it is appropriate to use a placebo in many of the clinical trials that are required in children. Usually it is more appropriate to compare a new drug with an established drug. Other ethical issues relate to the number of blood samples that are required and whether other methods can be used to avoid the need for invasive techniques[5].

Pharmacokinetic Studies in Children

It is essential that the numbers of blood samples required are kept to the minimum. The use of population kinetics, whereby a small number of blood samples are collected from an individual child but the total number of children studied is significantly increased, is being used more extensively[6]. It is not essential to determine every pharmacokinetic parameter. It may be more appropriate to calculate which pharmacokinetic parameter is of importance. Blood sampling at steady state of drugs delivered by a continuous intravenous infusion allows the determination of plasma clearance. Several groups have shown that this can be studied by using a single blood sample[7]. The individual needs to be able to determine the minimum number of samples required.

Analytical Methods

It is important that a basic understanding of the different analytical methods for determining drug concentrations in plasma or other body fluids is achieved. This will involve a knowledge of HPLC, GCMS and radioimmunoassay. The development of microassays is of particular importance in the field of paediatrics. The circulating blood volume in neonates and infants is considerably lower than that in adults.

Ontogeny of Drug Metabolism

The development of enzyme maturity varies for different metabolic pathways. P450 enzyme activity is usually reduced in the neonatal period. This may be increased in infants before reaching adult values in childhood. Glucuronidation is also usually significantly reduced in neonates, whereas sulphation may be increased. One needs to be aware of drug metabolism both in adults and in different stages of childhood. The inter-relationship between drug metabolism, efficacy and toxicity also needs to be understood.

Pharmacogenetics

Genetic differences in drug metabolising enzymes and/or receptors are increasingly being identified. The inter-relationship between pharmacogenetics and development is an area where there has been limited research. It is, however, important that this inter-relationship is understood for the safe and effective use of drugs in paediatrics. A greater understanding of the impact of pharmacogenetics in paediatric patients should both increase efficacy and reduce toxicity.

Non-invasive Methods

Both saliva and urine have been used as alternatives for blood sampling. Unfortunately, neither is popular with children. The caffeine breath test, which involves the use of a stable non-radioactive-labelled isotope of caffeine, has been shown to be useful for studying both drug interactions and the effect of disease on drug metabolism. This technique has been used in children as young as three years of age and also in neonates[8,9]. One needs to be aware of the availability of non-invasive methods.

Age-related Delivery Systems

Most adults prefer to take their medicine as tablets. This is impractical for young children. Suspensions are required and it is important that doctors in training understand the difficulties of preparing a medicine in an appropriate formulation. This is an area that has been studied predominantly by pharmacists, but medical input would be valuable[10]. In the field of asthma there are numerous inhalers for children of different ages. It is important that one understands the capabilities of children of different ages in relation to different inhaler techniques. The need to study drug delivery from these different inhalers is now being recognised by regulatory authorities.

Validity of Animal Models

There is a requirement from the FDA to carry out neonatal/juvenile toxicology studies. The rationale of validity of the use of animal models needs to be understood. Different animals have different levels of enzyme maturation. It is inappropriate to carry out toxicology studies in a juvenile animal and assume that a similar

scenario exists in the developing human. The differences and similarities between different animal models and the developing human is an area where more research needs to be carried out.

Pharmacodynamic Studies in Children

In the young child and neonate it may be difficult to assess pharmacodynamic effects. This is particularly important in the fields of pain and analgesia. Numerous pain scales have been developed which have been validated for children of different ages for different types of pain[11]. Understanding the development of these scales and the need for appropriate objective pharmacodynamic end points is crucial.

Neonatal Clinical Pharmacology

It is important to recognise that the study of clinical pharmacology in the neonate is very different to that in children. This is for a variety of reasons and includes differences in drug metabolism, pharmacodynamic response, and the lower circulating blood volume of the preterm newborn infant, in particular. Differences between premature and full-term neonates also need to be clearly understood.

Drug Toxicity

It is well recognised that drug toxicity in young infants and the fetus is considerably different from that of adults[12]. There have been numerous examples of age-related drug toxicity, e.g valproate hepatotoxicity in the young child, the metabolic acidosis as a consequence of use of propofol as a sedative in critically ill children and the grey baby syndrome owing to chloramphenicol. One needs to be able to link drug toxicity to drug metabolism in children.

Surveillance for Drug Toxicity

There is an increasing interest in surveillance for drug toxicity in children and the adaptation of models used for adults for use in children is to be encouraged. Adverse drug reaction surveillance in children has mainly been related to surveillance in hospital. This is in contrast to surveillance in adults where the majority of adverse drug reactions occur in the community. The individual needs training in proactive methods of drug surveillance involving both specific drugs[13] and groups of drugs or groups of patients[14].

Regulatory Requirements

It is important that individuals are aware that many medicines used in children have bypassed the licensing process[1–3]. With major changes introduced in the USA by the FDA and the new ICH guidelines on clinical trials in children, it is essential that trainees are fully aware of the moving goal-posts.

Situation in the UK

The United Kingdom at present has three paediatric clinical pharmacologists who are self-taught. There are two approved training posts, each for a single individual, in Great Ormond Street, London, and in Aberdeen. There are also plans to establish a post for training greater numbers of individuals in a shorter training programme in Derby and Nottingham.

Within the UK, clinical pharmacologists have responsibility for patients. The situation in the rest of Europe is different in that many countries' clinical pharmacologists do not have patients of their own. Within the UK it is important that, in new subspecialities such as paediatric clinical pharmacology, the individual is competent in both paediatrics and clinical pharmacology.

European Network for Drug Investigation in Children

In order to ensure adequate training, individuals may have to work in more than one centre. The European Network for Drug Investigation in Children includes the key paediatric clinical pharmacologists in Europe[15]. There is an agreement and understanding within the Network that individuals will offer training to junior doctors from other centres provided funding can be arranged.

In order to obtain more extensive training in certain aspects of paediatric clinical pharmacology, an individual is restricted to a handful of centres. For example, if one is to receive training in neonatal clinical pharmacology then it is best to contact one of the experts in this field, such as Professor Aranda or Professor John van den Anker, who have had papers published extensively in this area[16,17]. Similarly, if one desired experience in pharmacogenetics, then one should contact experts such as Professor Evelyne Jacqz-Aigrain in Europe or Professor Greg Kearns in the United States[18,19].

It is only by working together, both within Europe and, one would hope, within the USA, that we will be able to improve training in this developing area.

References

1. Turner S, Longworth A, Nunn AJ, Choonara I. Unlicensed drug use on paediatric wards. BMJ 1998;316:343-5
2. Conroy S, McIntyre J, Choonara I. Unlicensed and off label drug use in neonates. Arch Dis Child Fetal Neonatal Ed 1999;80:F142-F145
3. Conroy S, Choonara I, Impicciatore P, Mohn A, Arnell H, Rane A, Knoeppel C, Seyberth H, Pandolfini C, Raffaelli MP, Rocchi F, Bonati M, Jong G, de Hoog M, van den Anker J. Survey of unlicensed and off-label drug use in paediatric wards in European countries. BMJ 2000;320:79-82
4. Conroy S, McIntyre J, Choonara I, Stephenson T. Drug trials in children: problems and the way forward. Br J Clin Pharmacol 2000;49:93-7
5. Long D, Koren G, James A. Ethics of drug studies in infants; how many samples are required for accurate estimation of pharmacokinetic parameters in neonates? J Pediatr 1987;111:918-21
6. Thomson AH, Way S, Bryson SM et al. Population pharmacokinetics of gentamicin in neonates. Dev Pharmacol Ther 1988;11:173-9
7. Hughes J, Gill AM, Mulhearn H, Powell E, Choonara I. Steady state plasma concentrations of midazolam in critically ill infants and children. Ann Pharmacother 1996;30:27-30
8. Parker AC, Pritchard P, Preston T, Smyth RL, Choonara I. Enhanced drug metabolism in young children with cystic fibrosis. Arch Dis Child 1997;77:239-41
9. Pons G, Blais J, Rey E et al. Maturation of caffeine N-demethylation in infancy: A study using the $^{13}CO_2$ breath test. Pediatr Res 1988;23:632-6
10. Breitkreutz J, Wessel T, Boos J. Dosage forms for peroral drug administration to children. Paed Perinat Drug Ther 1999;3:25-33
11. Beyer J. Key issues surrounding the assessment of pain in children. Paed Perinat Drug Ther 1998;2:3-13
12. Choonara I, Gill A, Nunn A. Drug toxicity and surveillance in children. Br J Clin Pharmacol 1996;42:407-10
13. Norris E, Marzouk O, Nunn AJ, McIntyre J, Choonara I. Respiratory depression in children receiving diazepam for acute seizures – a prospective study. Dev Med Child Neurol 1999;41:340-43
14. Gill AM, Leach HJ, Hughes J, Barker C, Nunn AJ, Choonara I. Adverse drug reactions in a paediatric intensive care unit. Acta Paediatr 1995;84:438-41
15. van den Anker J, Choonara I. ENDIC – European Network for Drug Investigation in Children. Paed Perinat Drug Ther 1999;3:15-6
16. Aranda JV, Varvarigou A, Beharry K et al. Pharmacokinetics and protein binding of intravenous ibuprofen in the premature newborn infant. Acta Paediat 1997;86:289-93
17. Van den Anker J, Hop WCJ, Schoemaker RC et al. Ceftazidime pharmacokinetics in preterm infants: effect of postnatal age and postnatal exposure to indomethacin. Br J Clin Pharmacol 1995;40:439-43
18. Dervieux T, Medard Y, Baudoin V et al. Thiopurine methyltransferase activity and its relationship to the occurrence of rejection episodes in paediatric renal transplant recipients treated with azathioprine. Br J Clin Pharmacol 1999;48:793-800
19. Kearns GL. Pharmacogenetics and development: are infants and children at increased risk for adverse outcomes? Curr Opin Pediat 1995;7:220-33