Fourth International Workshop on Paediatric Clinical Trials

The fourth international workshop organised jointly by Paediatric and Perinatal Drug Therapy and The Association of Clinical Research Professionals was held in Toronto, Canada on 28th–29th September 2006. This was the largest workshop to date with over 60 registered delegates. There was excellent representation from the pharmaceutical industry, clinical research organisations and academia from the United States and Canada. There was extensive discussion on a wide range of issues at the workshop. There were five oral free communications which are shown below.

O1
Stimulation programmes for paediatric drug research – do children really benefit?

Isabelle Boots[1], Rám N Sukhai[1], Richard H Klein[2], Robert A Holl[1], Jan M Wit[1], Adam F Cohen[2], Jacobus Burggraaf[2]

[1]*Department of Paediatrics, Leiden University Medical Center, and* [2]*Centre for Human Drug Research, Leiden, The Netherlands*

Background: Most drugs that are currently prescribed in paediatrics have not been tested in children. Paediatric drug studies are stimulated in the USA by the paediatric exclusivity provision under the Food and Drug Administration Modernization Act (FDAMA) that grants patent extensions when paediatric labelling is provided. Similar legislation has recently been adopted in the European Union. We investigated the effectiveness of these programmes for expanding the use of medicines for children.

Methods: All drugs granted paediatric exclusivity under the FDAMA were analysed by studying the relevant summaries of medical and clinical pharmacology reviews of the pediatric studies, or if these were unavailable the labelling prescribing information as provided by the manufacturer. A systematic search of the literature was performed to identify drug utilisation patterns in children.

Results: From July 1998 to March 2006, 127 drug entities were granted paediatric exclusivity. Most frequent drug groups were anti-depressants and mood stabilisers, ACE inhibitors, lipid-lowering preparations, HIV antivirals and non-steroidal anti-rheumatics. The distribution of the different drugs closely matched the distribution of these drugs over the adult market, and not the drug utilisation by children.

Conclusion: Many drug studies in children have been executed since the introduction of the FDAMA; however, children infrequently use the drugs granted paediatric exclusivity. The priorities for paediatric drug research should be set by the need of the patients, not by market considerations.

O2
Clinical trials: the viewpoint of children

J Cherrill[1], H Hudson[1], C Cocking[1], V Unsworth[1], L Franck[2], J McIntyre[1], I Choonara[1]

[1]*Academic Division of Child Health, University of Nottingham, Derbyshire Children's Hospital, Derby, UK* [2]*Institute of Child Health, Great Ormond St Hospital for Children, London*

Background: There is growing recognition of the need for clinical trials in children. However, the views of children on this subject have not been explored. This is essential, particularly as the number of clinical trials involving children is set to increase due to changes in European legislation.

Methods: The study was approved by Derbyshire Research Ethics Committee. Children attending outpatients were initially approached by their consultant paediatrician and after giving informed consent were interviewed. The semi structured interviews incorporated subjects such as placebos, blood sampling, clinical trials, which conditions and medicines are important to study, rewarding children for taking part in research and also the consent process.

Results: Interviews were conducted with 30 children, ages 8–16 years (median 12 years). Nineteen of the children were receiving regular medication. Thirteen children had an understanding of where medicine came from including an 8 year old. Only three children all aged 16 years had a full understanding of the nature of clinical trials. Nineteen children recognised that there were risks involved with taking part in clinical trials and their ages ranged from 8 to 16 years. Children did not expect to be paid, as they felt it was in the interest of all children if they took part in a study. Seventeen children said, however, that they would take the money if offered, nine children would refuse the money and four were uncertain. Risks concerned with being paid were also recognised.

Conclusion: It is important to recognise that children are aware of medicines, how they are derived, their uses and the need to study them in relation to children. However, their knowledge of clinical trials is limited and further education is necessary. Children do have a view on being paid to take part in clinical trials, but are in the main happy to help, to the benefit of other children. Children's viewpoints should not be dismissed and an understanding of risk and their possible role in clinical trials, is evident in even the younger children interviewed.

O3
A comparison of paediatric clinical pharmacology training programmes in Canada and the UK

Mark Anderson[1], Imti Choonara[1], Michael Rieder[2]

[1]*Academic Division of Child Health, University of Nottingham, Derbyshire Children's Hospital, Derby, UK* [2]*Department of Paediatrics, University of Western Ontario, London, Ontario, Canada*

Background: There has been a long-recognised need for formal training programmes in paediatric pharmacology in order to facilitate the application of research to therapeutics in children. Canada has a long-standing programme, whereas the training programme based in the UK recently produced its first accredited paediatric clinical pharmacologist.

Methods: A direct comparison of the paediatric pharmacology training programmes overseen by the University of Western Ontario in Canada and the Royal College of Paediatrics and Child Health (RCPCH), in terms of entry point, duration and content. Information regarding content was derived from the "Draft Overall Goals and Objectives"

produced for the Pediatric Clinical Pharmacology Residency Training Program in Canada, and the curriculum for the RCPCH Training Programme in Paediatric Clinical Pharmacology in the UK.

Results: Entry point and duration: Doctors enter the two-year Canadian programme following three years of postgraduate core paediatric training. The three-year UK programme accepts doctors who have completed at least four years of postgraduate paediatric training.
Content: Both programmes contain objectives relating to the core areas of: pharmacokinetics; pharmacodynamics; drug toxicity and adverse drug reactions; design, conduct and interpretation of drug trials, including ethical and legal issues; and the drug development and regulatory process. Both programmes also have a strong emphasis on research. The Canadian programme also considers drug use and misuse in pregnancy.

Conclusion: Despite differences in entry point and duration, the content of the two training programmes in terms of learning objectives is very similar. Such similarities would facilitate international exchange programmes.

O4
The effect of N-acetylcysteine on ifosfamide-induced nephrotoxicity

Nancy Chen[1], Katarina Aleksa[3], Cindy Woodland[3,4], Michael Rieder[1,2] and Gideon Koren[1,2,3,4]

[1]Department of Physiology and Pharmacology, University of Western Ontario, London, Ontario, Canada [2]Department of Paediatrics, University of Western Ontario, London, Ontario, Canada [3]Division of Clinical Pharmacology and Toxicology, Hospital for Sick Children, Toronto, Ontario, Canada [4]Department of Pharmacology, Faculty of Medicine, University of Toronto, Toronto, Ontario, Canada

Background: Ifosfamide (IF) nephrotoxicity is a serious adverse effect in children undergoing chemotherapy. Previous studies have shown that in addition to the renal production of chloroacetaldehyde, a toxic metabolite of IF, lower levels of glutathione (GSH) may predispose the kidney to damages. The antioxidant N-acetylcysteine (NAC) is used extensively as an antidote for acetaminophen poisoning in children by replenishing GSH levels. As it has been safely and effectively used clinically, the objective of this study was to test whether reversal of ifosfamide-induced nephrotoxicity can be achieved by administering NAC. Supplementation with NAC may reduce or prevent the degree of cellular cytotoxicity induced by ifosfamide.

Methods: LLC-PK-1 cells were either pre-treated with NAC (0.4 mM or 2.5 mM) followed by or concurrently treated with 1 mM IF and 50 µM L-Buthionine sulfoximine (BSO). Cellular viability was assessed by alamarBlue™ assay at 96 hours. Intracellular GSH and GSSG levels were determined using a GSH/GSSG detection kit.

Results: There was a significant decrease of 60% in cellular viability when cells were treated with BSO and IF daily for 96 hours. This decrease was significantly reduced when cells were concurrently treated with NAC in a concentration-dependent manner. Intracellular and total GSH levels in cells receiving concurrent treatment of NAC were significantly higher than those without NAC treatment.

Conclusion: NAC protects renal tubular cells from ifosfamide-induced cytotoxicity. It is likely that NAC is protecting the cells by partially acting as a precursor for GSH synthesis. This mode of therapy may allow protecting children from life threatening nephrotoxicity induced by IF.

O5
In utero exposure to HMG-CoA reductase inhibitors; effects on fetal and neonatal outcome

N Taguchi, ET Rubin, A Hosokawa, ME Moretti, G Koren, S Ito

Division of Clinical Pharmacology and Toxicology, The Hospital for Sick Children, Toronto, Ontario, Canada

Background: Since HMG-CoA reductase inhibitors (statins) are widely used for the treatment of hyperlipidemia in women of childbearing age, the pregnancy safety data regarding statins are urgently needed. Recent case series based on voluntary reports described cases of malformations including central nervous system defects and unilateral limb defects. This raised concerns about the fetal safety of statins. The objective of this study is to determine whether gestational use of statins poses substantial fetal toxicity.

Methods:

- *Design* A prospective, observational cohort study with a comparison group.
- *Setting* A cohort based on a teratogen information service, The Motherisk Program.
- *Participants* The women with exposure to a statin during the first trimester were matched with pregnant women, who have contacted us for information on use of known *non*-teratogen during pregnancy.
- *Intervention* The data were collected by telephone interviews.

Results: Pregnancy outcome of 58 exposed to statins and 58 matched comparison group were followed. There was no significant difference in the rate of major malformations between cases (1/58) and controls (1/58) (P=0.46). The pregnancy outcomes, such as live birth (P=0.09), spontaneous abortion (P=0.49), and therapeutic abortion were not statistically different between the exposed and control groups.

Conclusion: Our pilot cohort did not demonstrate the malformation patterns reported in a case series based on voluntary reports.

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