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First International Workshop on Paediatric and Perinatal Drug Therapy and Paediatric Clinical Trials

The first international workshop in this area was held in Derby, UK on 15–16 June 2003. It was organised jointly by Paediatric and Perinatal Drug Therapy and The Association of Clinical Research Professionals. The aim was to bring together young investigators, the pharmaceutical industry and key senior investigators in the field. Twelve international speakers from Europe and North America led the sessions. Alongside the speakers there were 50 registered delegates whose backgrounds included paediatrics, clinical pharmacology, clinical pharmacy, clinical research organisations and the pharmaceutical industry. There were five oral free communications, which are shown below.

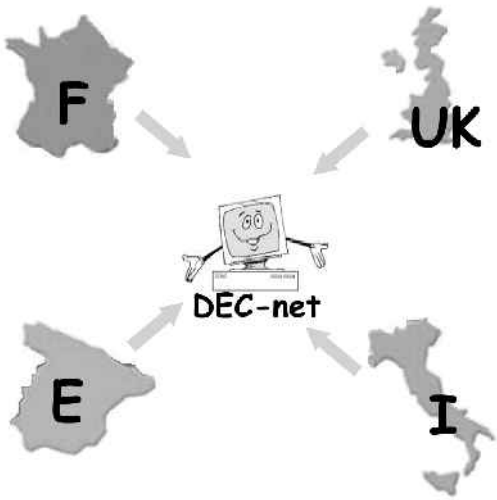
O1
A European, Paediatric, Clinical Trial Registry

C. Pandolfini[a], M. Bonati[a], H. Sammons[b], I. Choonara[b], E. Jacqz-Aigrain[c], I. Danés[d], I. Fuentes[d] and J. Arnau[d]

[a] *"Mario Negri" Institute for Pharmacological Research, Milan, Italy;* [b] *Derbyshire Children's Hospital, University of Nottingham, Derby, United Kingdom;* [c] *Hopital Robert Debre, Paris, France;* [d] *Fundacio Institut Catala de Farmacologia, Barcelona, Spain*

Background: The European Community, through its Fifth Framework Programme, decided to fund the development of a European registry of clinical trials in children in December 2002. The aim of the project is the creation of an online registry designed to handle essential data on paediatric, therapeutic clinical trials that can be expanded in the future to include data from all the European member states. The registry will be a tool for promoting and co-ordinating paediatric drug research throughout Europe and for identifying children's neglected therapeutic needs. The project began in January 2003 and involves members from France, Italy, the United Kingdom, and Spain. These groups have different, complementary, clinical backgrounds that will facilitate the registry's development.

Methods: The members are currently deciding which information will be collected and how, and will later begin to identify planned and ongoing trials through communication with ethical review boards, paediatrician associations, pharmaceutical companies, etc. The database is also currently being designed. Once trial data input begins, there will be a promotional phase during which health professionals and the public will be informed of the registry through means such as publications and presentations. The registry will then be activated and free access will be given after registration. At the end of the first year, a qualitative analysis of trial data will be performed.



Conclusion: Such a registry will hopefully aid in promoting communication and collaboration among researchers, facilitating patient recruitment, preventing trial duplication and inappropriate funding, and identifying therapeutic needs of children that remain neglected by clinical trials.

O2
Research in District General Hospitals and General Paediatrics in the UK. Fact or Fiction?

H.M. Sammons, J. McIntyre and I. Choonara

Academic Unit of Child Health, University of Nottingham, Derbyshire Children's Hospital, UK

Background: District General Hospitals (DGHs) see a large proportion of children in the UK with general paediatric problems. This study was to determine the extent research, published in the journal Archives of Disease in Childhood (ADC), is of a general paediatric nature and whether DGHs are involved in such research.

Methods: A hand searched review of the journal ADC for the years of 1997 and 2001, for original articles. Papers were then separated into UK based and non UK based for analysis of lead centre into tertiary centre, DGH or community based. All trials were analysed into single centre, multi centre or national data trials and RCTs per year were recorded. Lastly all papers were divided clinically into general paediatrics and specialities.

Results: Of the 152 papers published in 1997 and the 145 papers in 2001, 58% (1997) and 52% (2001) originated from the United Kingdom. Within these UK based studies; the 1997 cohort contained 75 papers (85.2%) from tertiary referral centres, 9 papers (10.2%) from DGHs and 4 papers (4.6%) from the community. In the 2001 cohort this had fallen to only 6.6% (5 papers) of articles with lead authors based in DGHs. 68 papers (90.6%) originated from tertiary referral centres and 2 papers (2.7%) from the community.

The number of multi centre trials, originating from the tertiary referral centres, increased from 7.2% to 15.9%. All of the trials carried out in DGHs were of a general paediatric nature and single centre trials. There were only 8 randomised controlled trials in the 1997 cohort, this rose to 13 in 2001. Over 50% of the papers involved an area of general paediatrics (55% and 62% in 1997 and 2001 respectively).

Conclusions: Most of the original research in the journal ADC has a tertiary centre as the lead and only a small number of papers are based in DGHs. The number of multi centre trials is rising but there is little involvment of DGHs. Research in DGHs needs to be encouraged as there is a large paediatric population who are being overlooked and this may help recruitment which is known to be difficult within the paediatric field.

O3
Computerized CPR Drugs Sheet for Pediatric Patients as a Tool to Improve Efficacy and Safety in Children

L. Matok, I. Levin, M. Adam and A. Vardi

Department of Pharmacy Services and the Department of Pediatric Critical Care Medicine Safra's Children Hospital, The Chaim Sheba Medical Center, Tel-Hashomer, Israel

Background: Cardiopulmonary resuscitation (CPR) in children requires the calculation of CPR drug doses according to the child's age and weight. This takes time and is a source of errors. In order to be prepared, it is customary in pediatric critical care and in some of the emergency departments to prepare a pre-calculated CPR drug sheet.

The time needed to prepare a manually calculated CPR drugs' sheet (including double checking of the calculations) is about 30 minutes, and the process is not error free.

Purpose: The study was conducted in order to check whether the use of a computer software that calculates the CPR drug doses according to the child's age and weight would enable to save time and abolish errors. A secondary purpose was to check whether profession, age, seniority and the department to which the staff belongs have influence on the results.

Methods: A comparison was made between 128 manually calculated CPR drug sheets calculated by 64 staff members (nurses and physicians from PICU, NICU and pediatric emergency departments) and 100 CPR drugs' sheets calculated by a special software developed for that purpose. The preparation time of the sheet and the number of errors were checked.

Results: The average time to prepare the manually calculated CPR drug sheet was 14.7 minutes (±5.3 minutes), the number of calculation errors was 3.7 (±2.27). The average time to prepare the CPR drug sheet was 2.27 minutes (±0.6 minutes) and the number of calculation errors was 0.

Several factors influenced the number of calculation errors in the manually calculated CPR drug sheet: Minimum and maximum doses that were not accounted for, long preparation time, and the education and seniority of the staff.

Conclusion: The CPR drug software enables time saving for the medical and paramedical staff and improves the quality and safety of work by abolishing calculation errors.

O4
Prediction of the Age Related Changes in Drug Clearance in Children

T.N. Johnson, A. Rostami-Hodjegan and G.T. Tucker

University of Sheffield Section of Molecular Pharmacology and Pharmacogenetics, Royal Hallamshire Hospital, Sheffield, S10 2JF, UK

The SIMCYP® software developed at the University of Sheffield is designed to incorporate genetic, physiological, demographic and clinical variability into *in vitro–in vivo* extrapolation, thus providing data for a variety of patient groups, including 'at risk' as well as 'average' individuals. SIMCYP® has previously been successfully applied in the prediction of drug interactions[1,2] and clearance values[3] in an adult population.

A number of factors contribute to developmental changes in metabolic drug clearance in children. These include relative liver size, liver blood flow, protein binding and the maturation of individual drug metabolising enzymes. Many of the variables are defined for children in the SIMCYP® software. Information on the ontogeny of specific cytochrome P450 enzymes suggests that most of the values for enzyme abundance (expressed as pmol/mg microsomal protein) are near to adult levels by 1 to 2 years of age.

We have applied *in vitro–in vivo extrapolation* approaches to predict clearances in different paediatric populations older than 2 years. The age-related clearance of a number of drugs commonly used in children have been studied, including midazolam, caffeine, diclofenac, omeprazole and carbamazepine. So far, we have obtained close agreement between observed and predicted values (r^2 = 0.94, 0.82, 0.96, 0.7 and 0.77 respectively) and also associated variability

Incorporating further information on physiological development and the ontogeny of CYP enzymes into the SIMCYP® model is expected to allow prediction from birth to 2 years. Once validated the model will have a number of applications including dosage prediction and the design of clinical studies in children.

1. Yang *et al.* Br J Clin Pharmacol, 2001; 52: 472P
2. Yang *et al.* Br J Clin Pharmacol, 2002; 53, 438 – 439P
3. Proctor *et al.* Pharmacology (Suppl. 1): LB87
4. Hines RN, McCarver DG, J Pharmacol Exp Ther 2002; 300: 355 – 360.

O5
Administration Errors in Four French Paediatric Units: Preliminary Results

S. Prot[a], A. Goron[a], J.-Eudes Fontan[a], C. Alberti[b], O. Bourdon[a], S. Gottot[b] and F. Brion[b]

[a]*Service de Pharmacie, Hôpital Robert Debré, Paris, France*

[b]*Service de Santé Publique, Hôpital Robert Debré, Paris, France*

Background: Paediatric patients represent a high risk group for administration mistakes. Many drugs are unlicensed or used off-label, and often available only in adult dosage. Few reports of these errors are available in the literature. The aim of our study was to assess the frequency and the type of administration errors in paediatric units.

Method: Administration errors were detected by the observation method in four clinical units of a paediatric university hospital in Paris, France, from April 2002 to March 2003. The direct observations were made by a pharmacy resident or students every morning from Monday to Friday. An error was defined as any discrepancy between the physician's order and the administration.

Results: 336 patients were included (median age: 5 months, 60% of male) and 1719 administrations were followed. At least one administration error occurred in 24.8% of cases (18% to 34% among the different units). The most frequent errors concerned time (10.8% delayed from more than 1 hour), route (5.8%), dose (4.1%), dosage (1.4%), omission (1.6%) and unauthorized administered drugs (0.9%). 55% of nurses that performed the administrations were graduate since 1998 and 48% were in the units for less than 2 years. More than 40% of the administered drugs were vitamins, antibiotics and treatment against anaemia.

Conclusions: These results are especially valuable because they provide data from paediatric teaching hospital. The clinical significance of those errors will be judged by an expert panel of physicians and their determinants will be evaluated to prevent them.