Fifth International Workshop on Paediatric Clinical Trials

The fifth international workshop organised jointly by Paediatric and Perinatal Drug Therapy and The Association of Clinical Research Professionals was held in Derby, UK on 18th–19th June 2007. There were over 50 registered delegates who came from Europe, North America, Australia and New Zealand. The meeting covered the practical aspects of paediatric clinical trials as well as advances in paediatric clinical pharmacology including pharmacogenetics, medication errors and trials of antidepressants. There were seven oral free communications which are shown below.

O1
Contributors to inter-individual variability of the phenotypic *O*-demethylation activity in the first months of life

K Allegaert[1], RHN van Schaik[2], JN van den Anker[3,4,5], V Cossey[1], R Verbesselt[6], C Vanhole[1], J de Hoon[6]

[1]Neonatal Intensive Care Unit, Department of Paediatrics, University Hospital, Gasthuisberg, Leuven, Belgium; [2]Department of Clinical Chemistry Erasmus MC, Rotterdam, The Netherlands; [3]Department of Paediatrics, ErasmusMC, Sophia's Children Hospital, Rotterdam, the Netherlands; [4]Division of Pediatric Clinical Pharmacology, Children's National Medical Center, Washington, DC, USA; [5]Departments of Pediatrics, Pharmacology and Physiology, The George Washington University School of Medicine and Health Sciences, USA; [6]Center for Clinical Pharmacology, University Hospital, Gasthuisberg, Leuven, Belgium

Objective: To assess the impact of various co-variables on *in vivo* phenotypic *O*-demethylation activity during the first months of life.

Methods: Plasma time-concentration profiles of tramadol (M) and *O*-demethyl tramadol (M1) in the first 24 h of continuous intravenous M administration were collected. M and M1 concentrations were determined by High Performance Liquid Chromatography. CYP2D6*3, *4, *5 and *6 variant alleles, as well as gene duplication analyses were performed on genomic DNA isolated from EDTA blood, using validated PCR-RFLP assays. Correlations between potential co-variables [postmenstrual age (PMA), postnatal age (PNA), number of CYP2D6 active allele(s)] and the plasma log M/M1 were investigated.[1,2]

Results: Based on 137 plasma samples collected in 20 patients (25-53 weeks PMA), mean plasma log M/M1 was 0.84 (SD 0.39). A significant correlation between plasma log M/M1 and PMA (r = –0.73, $P<0.0001$) and PNA (r= –0.58, $P<0.005$) were observed. Log M/M1 was significantly higher in patients with 1 compared to patients with > 1 active CYP2D6 alleles. In a multiple regression model, PMA and CYP2D6 active allele frequency independently contributed to the log M/M1 variability.

Conclusions: *O*-demethylation activity was already observed in early life. In addition to PMA, CYP2D6 variant allele frequency significantly contributed to the inter-individual variability in log M/M1. CYP2D6 polymorphism therefore already contributes to the inter-individual variability in phenotypic *O*-demethylation in early life.

References:

1. Allegaert et al. Br J Anaesth 2005;95:231-239
2. Allegaert et al. Eur J Clin Pharmacol 2005;61:837-42

O2
No evidence of a relationship between pharmacokinetics and pharmacogenetics of tacrolimus in renal transplant children

V Elie[1], C Monchaud[1], M Fakhoury[1], Y Medard[1], S Azougagh[1], V Leroy[2], E Jacqz-Aigrain[1], DIVAT Paediatric Network[3]

[1]Department of Paediatric Clinical Pharmacology and Pharmacogenetics; [2]Department of Paediatric Nephrology, Hôpital Robert Debré, Paris, France; [3]Department of Paediatrics, Hospices Civils de Lyon, Hôpital Edouard Herriot, Lyon, France

Background: Tacrolimus (FK506) pharmacokinetic (PK) variability can be explained by pharmacogenetics (PG). This study described early FK506 PK and searched for a PG/PK relationship in a pediatric renal transplant setting.

Methods: This subanalysis of a French national database (DIVAT) included FK506 PK profiles at one month post-transplantation from 19 children aged 12.4±5 years. FK506 was assayed in whole blood using EMIT® and area under the concentration-time curve over 12 hours (AUC_{0-12}) was calculated. Genotyping was carried out by Taqman™ on mutations of the genes coding for: CYP3A4 (CYP3A4*1), CYP3A5 (CYP3A5*3), P-gp (MDR1: C1236T, G2677T, C3435T) and MRP2 (ABCC2: C-24T, G1249A, T3563A, C3972T). Relationship between AUC_{0-12}/dose and PG profile was tested.

Results: Patients received a FK506 dose of 0.11±0.05 mg/kg (0.03–0.2). Mean AUC_{0-12} was 220±100 h.µg/L and mean AUC_{0-12}/dose was 0.08±0.07 h/L (0.02–0.31). 18/19 had the SNP (Single Nucleotide Polymorphism) CYP3A5*3/*3 or CYP3A4*1/*1, coding for a nonfunctional and a functional protein respectively. The majority of patients were heterozygous for the MDR1 C3435T mutation (C/C: 42.1%, C/T: 52.6%, T/T: 26.3%) and a linkage disequilibrium between the three MDR1 SNPs was demonstrated. ABCC2 genotypes showed a minority of mutant homozygous (5.3–10.5%). No significant relationship between PK AUC_{0-12}/dose and any SNP could be evidenced.

Conclusion: This study confirmed the wide PK variability of FK506 and failed to show a relationship between PK and PG, probably because of the small number of patients. More patients need to be recruited to test PK variability based on SNPs combinations.

O3
Clinical trials: the viewpoint of school 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 Street Hospital for Children, London, UK

Introduction: The number of clinical trials involving children is set to increase due to changes in European legislation. The views of children in hospital, on this subject, have been explored[1]. The views of healthy children however, have not been studied.

Methods: The study was approved by Derbyshire Research Ethics Committee. Children attending a local secondary school were initially approached with a letter regarding the project and consent to take part. The questionnaire incorporated subjects such as placebos, blood sampling, clinical trials, prescribing, which conditions and medicines are important to study, rewarding children for taking part in research, scenarios of possible trials and also the consent process.

Results: 123 questionnaires were completed with children, ages 11–16 years (median 13 years). 19 were receiving regular medication. 36 had heard of the term clinical trial, and 29 were able to explain the term. 74 stated that they thought children should be involved with the testing of medicines, and 63 said that children may like to take part in the testing of medicines to help others. Children had a good comprehension of possible risks and felt that those that take part in clinical trials should be informed of any possible side effects. Nevertheless, 62 children would be more likely to take part in clinical trials if they were paid to do so.

Discussion: An understanding of possible risk and a child's role in clinical trials is evident amongst healthy school children. Their compliance is essential in order that research into paediatric medicine is advanced. The protection of children in clinical trials is now law, and it is important that we include children in on going decisions that are made.

References:

1. Cherrill J et al. Paed Perinat Drug Ther 2006;7:144

O4
The DEC-net European register of paediatric drug therapy trials: its contents and their context

C Pandolfini[1], M Bonati[1], V Rossi[1], E Santoro[1], C Naylor[2], H Sammons[2], I Choonara[2], S Zarrabian[3], E Jacqz-Aigrain[3], JM Castel[4], I Danés[4], I Fuentes[4], J Arnau[4]

[1]"Mario Negri" Institute for Pharmacological Research, Milan, Italy; [2]Derbyshire Children's Hospital,University of Nottingham, Derby, UK; [3]Hopital Robert Debre, Paris, France; [4]Fundació Institut Català de Farmacologia, Barcelona, Spain

Background: The lack of suitable paediatric trials and drug information has been thoroughly documented. DEC-net, the European register of clinical trials on medicines for children, was a 3-year pilot project activated in 2004 to help make those involved in paediatric health aware of ongoing trials. DEC-net's contents were analysed to assess which paediatric health areas are covered by research and by which trial types.

Methods: The contents were analysed. The disease areas reflected were also compared with those covered by published trials and with Global Burden of Disease (GBD) data.

Results: In all, 257 trial records were analysed, 86 of which were entered by the Italian partner, 84 the UK, 56 the French, and 31 the Spanish. Spain had a majority of multi-national trials, the UK a majority of single-centre national trials. Most were experimental (79%). The most commonly represented diseases were neoplasms (14% of trials); the most common drugs were antineoplastic/immnomodulating agents (26%). In all, 28% were double-blind RCTs. The most common disease areas were similar to the published trials' areas. Contrarily, the primary research area was low on the GBD list.

Conclusion: International research efforts exist, even for paediatrics, although there may be an imbalance between national and multinational studies and a limited approach to double blind RCTs. Recent initiatives will increase the number of children participating in research, but paediatric research priorities need to be better defined. This can be done by registering research and making the information available to all relevant actors.

O5
Anti-asthmatic drug prescriptions in Italian children and adolescents

Marina Bianchi, Antonio Clavenna, Lorena Labate, Maurizio Bonati

Laboratory for Mother and Child Health, "Mario Negri" Institute for Pharmacological Research, Milan, Italy

Background: Asthma is the most common chronic disease in childhood. A study was therefore performed to estimate the prevalence and evaluate the appropriateness of anti-asthmatic drug prescriptions in an Italian paediatric population.

Methods: Drug prescriptions involving 24,407 children <18 years old, dispensed during 2003 by the retail pharmacies of the local health unit in Lecco, Italy, were analysed. Children ≥ 6 years old receiving anti-asthmatics were categorised into three subgroups based on the number of boxes prescribed: occasional, low (2–3 boxes) and high users (≥ 4 boxes). A logistic regression analysis was performed to estimate the relationship between the drug use patterns and formulations, antibiotic co-prescriptions, systemic steroid prescriptions and rate of hospitalisation.

Results: Anti-asthmatic drugs were prescribed to 6,594 (12%) children and adolescents; 56% of whom received only one box of drug. Prevalence varied according to age, with the highest values at 1 and 4 years (24 and 21%, respectively), which decreased to 3% in adolescents 17 years old. Inhaled steroids were the most frequently prescribed drugs (83%). The most common was beclomethasone. Occasional, low and high users represented 58, 29 and 13%, respectively, of the treated population ≥ 6 years old. High users were found to be at increased risk of systemic steroid prescriptions (OR 8.6) and hospital admission for asthma (OR 6.8).

Conclusion: This study confirms that anti-asthmatic drugs are over-prescribed in Italian children. Moreover, this approach seems to be effective in estimating asthma severity and appropriateness of the therapies.

O6
Maturation of GFR in children

M Rhodin, BJ Anderson, NHG Holford, GFR Collaboration Group

University of Auckland, New Zealand

Background: Drug elimination through the kidney is a major clearance pathway. The description of renal function maturation is influenced by covariates such as age and size. There is not a simple linear relationship between maturation and age. The aim of this project was to search for data that could be used to build a model for the prediction of renal function maturation with age.

Methods: The database comprised measured GFR (using inulin, ^{51}Cr-EDTA, Tc^{99m}-DTPA or iohexol) from eight studies (n=923) and involved premature neonates (22 weeks postmenstrual age) to adulthood (31 years). A nonlinear mixed effects approach (NONMEM) was used to examine the maturation of renal function. Size was the first covariate and GFR was standardised for a body weight of 70 kg using an allometric ¾ power model.

Results: Postmenstrual age was a better descriptor of maturational changes than postnatal age. A sigmoid Emax model best described the nonlinear relationship between GFR maturation and postmenstrual age. GFR increased with a 50% maturation half-time of 46.4 post menstrual weeks (95%CI 43.7–48.5) to reach 91% of adult rates (114 95%CI 109–118 mL/min/70kg) at 1 year of life. The Hill coefficient was 3.43 (95%CI 3.1–3.5).

Conclusion: Renal function can be expressed as a fraction of a typical standard adult GFR. We propose that this can

lead to a clearer understanding of the relationship between biomarkers such as serum creatinine and renal function in the very young so that renal function can be assessed independently of the predictable changes with age and weight.

O7
High dose methotrexate in paediatric acute lymphoblastic leukemia: impact of transporters pharmacogenetic polymorphisms on pharmacokinetics

T Adam de Beaumais[1], M Fakhoury[1], D Zhang[1], Y Medard[1], S Azoughah[1], K Yacouben[2], E Jacqz-Aigrain[1]

[1]Department of Paediatric Pharmacology and Pharmacogenetics, [2]Department of Haematology, Robert Debre Hospital, Paris, France

Background: Children with acute lymphoblastic leukaemia (ALL) are treated according to EORTC 58951 protocol in Robert Debre Hospital. This study was conducted to explore the impact of the genetic polymorphisms of methotrexate (MTX) transporter (RFC1) and/or efflux proteins (MDR1 and MRP2) on the inter-individual pharmacokinetic variability of high dose MTX (HD-MTX (5g/m^2)).

Methods: 65 children received three or four HD-MTX courses during interval phase therapy according to their risk group. MTX plasma level was assayed using EMIT® technique. Area under the concentration-time curve ($AUC_{0-\infty}$) from the start of the infusion was calculated for each cure according to a previous population based pharmacokinetic study. Genetic variants in RFC1 (G80A), P-glycoprotein (MDR1: C1236T, G2677T, C3435T) and MRP2 (ABCC2: C-24T, G1249A, T3563A, C3972T) were determined by real-time PCR (Taqman™).

Results: This study showed a high intra-individual variability of AUC/dose between courses and values from the first course (AUC1/dose) were used for statistical analysis. The linkage desequilibrium between MDR1 mutations described in the literature was observed in our population. Homozygous mutant patients for RFC1 (33.7%) or MDR1 (17.3%, 15.3%, 19.4%, 10.7% for the three mutations) genotypes showed a tendency for higher AUC1/dose levels than heterozygous or wild type patients. Only MDR1 C3435T reached statistical significance (P=0.023). MRP2 polymorphisms were not significantly related to MTX AUC1/dose.

Conclusion: The present data suggest that RFC1 (G80A) and MDR1 (C1236T, G2677T, C3435T) genes polymorphisms contribute to inter-individual variability in response to HD-MTX. The identification of MDR1 C3435T polymorphism may be a useful tool to optimise MTX therapy.

Published Online: 10 August 2007
doi:10.1185/146300907X199830