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

The second international workshop in this area was held in London, Ontario, Canada on 15–16 October 2004. It was organised jointly by Paediatric and Perinatal Drug Therapy and The Association of Clinical Research Professionals. Fourteen international speakers from North America and Europe led the sessions. Alongside the speakers there were just under 50 registered delegates, the majority of whom were trainees in paediatrics and clinical pharmacology. There were three oral free communications and two posters, which are shown below.

O1
Why do parents consent for their children to participate in paediatric research?

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Objectives: To assess what motivates parents to consent to a randomised clinical trial (RCT) and the factors that influence their decisions to take part in a future studies.

Methods: A multi-centre randomised equivalence trial of oral versus IV treatment for community acquired pneumonia in children. A postal questionnaire was sent to the parents of the 243 children recruited.

Results: 131 questionnaires were returned, response rate 55.5% (seven addresses were incorrect). 98% of parents remembered consenting, 95% felt they had enough time to make their decision and 95% felt they received enough information. The major reason given for participating was given as benefit to other children 32%, contribution to science 27%, benefit to their own child 19%, and others 23%. 61% felt there was an advantage to taking part. Of these 59% felt the advantage was to the childhood population in the future whereas 36% felt the advantage to be for their own child. 17% felt there was a disadvantage to taking part and 18% felt obliged to participate. 93% said they would take part in a similar study in the future. Factors influencing this being benefit to their own child (92%), benefit to all children (88%), contribution to medical science (82%), and study design (80%).

Conclusion: The major motivation in parents consenting for their child to participate in an RCT was to increase medical knowledge in the future. Most saw an advantage in taking part in the trial and would take part in future paediatric research.

O2
Intravenous microdialysis as a tool for pharmacokinetic and pharmacodynamic drug investigations in humans

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Due to the maturation of organs being responsible for drug metabolism and drug response, pharmacokinetic (PK) and pharmacodynamic (PD) data are critically important for improving drug therapy in children. Sparse data sampling and subsequent population pharmacokinetic analysis, however, have some limitations in the practical application because inaccurate documentation and non-compliance of the patients might prevent a proper analysis and interpretation of data.

The aim of our study was to use a different approach by developing an intravenous microdialysis technique to quantify drug concentrations in human plasma providing rich data sets with blood free determination of drug concentrations. An *in vitro* microdialysis cell was designed and issues like loss of dialysate, retrodialysis by calibrator and relative recovery were addressed to delineate optimal *in vivo* intravenous microdialysis conditions for the test drug sotalol. These conditions were then applied in an *in vivo* study to six healthy volunteers. They ingested an oral dose of 160 mg sotalol and for comparison conventional plasma samples and intravenous microdialysates were collected for 24 hours. Dialysates and plasma samples were analysed using a validated HPLC assay. The pharmacokinetic parameters Cmax, tmax, *t*? and AUC were calculated from microdialysate and plasma concentration/time profiles. As a pharmacodynamic parameter heart rate corrected QT interval was determined from 12 lead electrocardiogram stripes, recorded up to 4 times per hour to assess the dose-dependent QT-interval-prolongation of sotalol. Finally, pharmacokinetic/pharmacodynamic modelling was performed using a linear direct link model.

Comparing the pharmacokinetic and the pharmacodynamic parameters gathered from both methods revealed no significant differences between the conventional and microdialysis method. Therefore, this technique might be an additional tool to perform pharmacokinetic and pharmacodynamic investigations and might be further improved for the paediatric population.

O3
Are antioxidants effective in preventing fetal alcohol spectrum disorders?

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Background: Affecting 0.5–3 of 1000 births, Fetal Alcohol Syndrome (FAS) is the most preventable birth defect. A systematic review of antioxidant therapies in animal studies suggests that they may attenuate the damaging effects of ethanol exposure to the fetus.

Objective: The primary objective is to compare the effectiveness of high doses of vitamins C and E in combination with folic acid with the supplementation of prenatal vitamins in mitigating the adverse effects of alcohol consumption during pregnancy. The secondary objective is to assess the incremental cost-effectiveness of the treatment.

Hypothesis: High doses of vitamin C (1g), vitamin E (400 IU), in addition with folic acid (800 mcg) contained in prenatal vitamins are effective in attenuating adverse fetal effects of ethanol.

Methods: 189 women will be randomised into a doubled-blinded, placebo controlled trial in 1–1–1 a balanced design, stratified by pregnancy stage at start of enrolment (0 to ≤6,

6 to ≤12, and 12 to ≤24 weeks). Eligible women will be randomised into one of three groups: high dose of vitamin C and E with folic acid; placebo with folic acid; or counselling from Motherisk staff to use a prenatal multivitamin containing folic acid. All women will be encouraged to discontinue drinking. All patients will be seen in the Motherisk clinic every two months and contacted by phone throughout their pregnancy. All babies will be assessed after delivery and evaluated at three, six, and fourteen months of age.

Results: The study was launched in February 2004.

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P1
Isotretinoin use in pregnancy

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Background: Isotretinoin (Accutane) has been identified as one of the most potent human teratogens, causing birth defects in more than 35% of babies exposed during pregnancy. The manufacturer, Hoffmann-La Roche was aware of significant fetal risk and voluntarily instituted the Pregnancy Prevention Program (PPP). Over the past several years, however, Teratology Information Services noted an increase in the number of pregnant women exposed to isotretinoin who contacted their centres.

Objectives: To assess indications for isotretinoin treatment. To identify causes of failure to prevent pregnancy while on treatment. To examine pregnancy outcome. To develop new guidelines and additional requirements in order to prevent pregnancies while on isotretinoin treatment.

Design: Prospective survey using questionnaires.

Methods: Three phone interviews following verbal administration of informed consent. The information was collected during intake interview following interim (1 month later) and outcome interviews (after expected delivery date).

Preliminary results: 12 women were enrolled (February 2001–February 2004), age 18–39 years. One was diagnosed as acne and five had a prescription written by a dermatologist. Seven were treated with antibiotics before isotretinoin prescription. In response to questions about compliance of elements of PPP: Only four women had two negative pregnancy tests before receiving a prescription. Only one woman used two forms of birth control simultaneously, starting one month before receiving prescription. Four women received a pregnancy test each month before refilling their prescriptions. Two signed a consent form.

Pregnancy outcome: Five live births, one isotretinoin embryopathy, four therapeutic abortions, one miscarriage, two still pregnant.

Preliminary conclusions: Isotretinoin is prescribed inappropriately. Failure to prevent pregnancy is not compliant with the current PPP requirements. One in four live births was dysmorphic. Our study provides important data that may help design more effective prevention strategies.

P2
Determination of methadone and its metabolite, EDDP, in breast milk by gas chromatography

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Introduction: Methadone in plasma passes through unchanged into breast milk (BM) posing a question as to the safety of its use during breastfeeding. Am. Acad. of Pediatric state that daily methadone doses of ≤20 mg are compatible with breastfeeding. However, women in methadone programs are on much higher doses. High fat content in BM poses interesting challenges in the analysis of drug analytes.

Objectives: To develop a BM extraction technique that is viable in the extraction of drugs and their metabolites using methadone and EDDP as model compounds.

Methods: Calibration standards were made using blank human BM. Six sequentially collected BM were analysed to study methadone elimination in one opiate-dependant new mother.

Results: After liquid–liquid extraction, to reduce the fat content the extract was filtered through "Amicon Ultrafee-MC centrifugal devices". This resulted in a clear extract that could be concentrated and injected into a GC. The calibration curve for both Methadone and EDDP were reproducible and linear, methadone r=0.999 and EDDP r=0.996. In the BM of the patient, the time to peak for methadone and EDDP was about 3 h and $t_{1/2}$ for both was about 4 h. Using the peak BM methadone levels, the baby over a 24 h period would get 300 mcg.

Conclusions: Filtering the BM extract through the Amicon Ultrafree MC centrifugal device gave a clear extract that could be injected into a GC. Using this method to remove fat gave linear calibration curves that could be reproduced over many days. This method can be adapted to other drug assays in breast milk.