Third International Workshop on Paediatric Clinical Trials

The third international workshop organised jointly by Paediatric and Perinatal Drug Therapy and The Association of Clinical Research Professionals was held in Derby, UK on 11th-12th July 2005. The workshop was highly successful with fifteen international speakers from Europe, North America and New Zealand. Among the forty registered delegates, there was a good mix of trainees in paediatrics and clinical pharmacology, paediatric clinical pharmacists and investigators from the pharmaceutical industry and clinical research organisations. There were ten oral free communications which are shown below.

O1
A primary analysis of the first European, paediatric clinical trial register, DEC-net

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Background: DEC-net, the first register of planned, completed, and ongoing drug therapy paediatric clinical trials was activated in July 2004. It is run by four groups (France, Italy, Spain, UK) who input data on trials being run in their country. DEC-net can be freely consulted in different languages (www.dec-net.org). To evaluate aspects of the trials inputted so far, a primary, descriptive analysis of the first 10 month period was performed.

Results: A total of 118 trials were included, 25 from France, 20 from Italy, 13 from Spain and 60 from the UK. In all, 32 were multinational trials, of which 29 involved >1 of the register's participating countries and 6 all four. The majority were experimental (97), controlled (70), and randomised (69). In all, 26 studies (22%) were randomised, controlled, double-blind trials and mainly involved children and adolescents with cystic fibrosis and allergic rhinitis. Half of the experimental trials were phase III. The most common diseases addressed were leukaemia (13 trials) and HIV (10), and, consequently, antineoplastic agents were the most common experimental drugs.

Conclusion: This first evaluation demonstrates that clinical trials in children are currently running, even if often ignored. Awareness of ongoing studies can stimulate interaction and collaboration, also on the international level. When the register reaches an adequate size, further analyses will allow the identification of neglected, paediatric therapeutic areas.

O2
Neonatal outcome following pregnancy exposure to antidepressant drugs. A case-control study based on longitudinal database.

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Background: Although antidepressants, especially the selective serotonin reuptake inhibitors (SSRIs), have been commonly used off-label during pregnancy for years, their safety on the fetuses and newborns is widely debated, in particular with respect to neonatal withdrawal symptoms. A case-control study comparing the characteristics (birth weight, gestational age, side effects) of neonates exposed/non-exposed to antidepressants in utero was performed.

Methods: From our Drug Information Centre database we selected, as cases, women who took antidepressants during pregnancy and delivered live born children between 1995-2003. Each case was matched for maternal age and gravidity to 6 randomly selected controls (not exposed to teratogenic drugs or drugs known to cause neonatal side effects, such as beta-blockers or benzodiazepines). Odds ratio was estimated for attributable risks.

Results: Of the 200 neonates exposed to antidepressants in utero, 14 had adverse events and 3 required hospitalisation. Jaundice (n=5), agitation (n=3) and respiratory distress (n=2) were the most common symptoms. In the control group, 46 newborns had side effects and no statistically significant differences in the prevalence rate compared to the exposed group were found, even after stratification for drugs or length and pregnancy period of exposure. Only the prematurity rate was significantly higher in exposed compared to non-exposed newborns (OR= 1.99; 95% CI 1.12-3.41).

Conclusion: These results do not support an association between antidepressant exposure and unsafe fetal and neonatal outcomes in newborns. However a risk-benefit balance on an individual basis is needed when considering antidepressant therapy during pregnancy, although long term effects should be adequately evaluated.

O3
Characterisation of an extemporaneous tacrolimus suspension

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Background: Since there is no licensed liquid dosage form for the immunosuppressant tacrolimus, an extemporaneous suspension (0.5 mg/ml in Ora plus ◆ : simple syrup 1:1) had been developed for paediatric use and was shown to be chemically stable for 8 weeks. However, poor bioavailability (50% lower than that of the capsule) has been reported [1]. Plasma levels of tacrolimus were also reported to be erratic and corresponded to an increase of graft rejection [2]. As it was not clear if these problems could be linked to formulation factors, the purpose of our work was to study the physical property and dose uniformity of the suspension.

Methods: Suspensions were custom made by a special manufacturer. Laser diffraction and light microscopy were used to characterise the particle size. Drug contents were measured using HPLC.

Results: No significant change in particle size was detected over the period studied. The dose uniformity was good at large dose levels, but extremely erratic at low dose levels.

Conclusion: The suspensions were physically stable and good dose uniformity was observed at large dose levels. However, at low dose level, dose uniformity varied significantly, which could contribute to the observed erratic plasma levels.

Acknowledgement: This work is supported by an unconditional grant from Fujisawa (UK).

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2. Van Mourik et al. 3rd Int Congress Immunosuppression 2004. San Diego, USA

O4
A taste-testing study in healthy children to investigate preference for ibuprofen suspension or placebo

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Background: To identify the extent to which the taste of ibuprofen is masked in commercially available ibuprofen suspension and to measure the influence of the 'ibuprofen taste' on children's preference in comparison with placebo.

Methods: Parental informed consent was collected and children were screened by a physician before entering the study. 151 children aged 4-7 years tasted 2 suspension samples: ibuprofen 5 mg/ml and matched placebo, in a randomised order. Children received a volume equal to the recommended over-the-counter dose of ibuprofen suspension (7.5 ml for 4 - 6 year olds and 10 ml for 7 year olds). After tasting each sample, children indicated how much they liked that sample on a 10 cm visual analogue scale (VAS) depicted with a 'sad face' at the beginning of the scale and a 'happy face' at the end, and described what they liked or disliked about the sample. After tasting both samples, children were asked whether they could distinguish between the samples and, if so, which they preferred, and why.

Results: Mean (SD) VAS scores, measured from the 'sad face' end, were 6.78 (3.49) and 7.13 (3.42) for ibuprofen and placebo, respectively (p = 0.38). Only one child mentioned a 'burn' sensation. 84% of children could distinguish between the samples and, of these children, 58% preferred placebo and 42% preferred ibuprofen (p = 0.07). Preference for the placebo was driven by a perception of sweetness compared with the ibuprofen suspension.

Conclusions: There were no significant differences between ibuprofen and placebo in any parameter assessed, suggesting that the formulation effectively masks the taste of raw ibuprofen. The 'burn' characteristic does not appear to be a significant factor in driving taste preference.

O5
GABA excitation and neonatal midazolam

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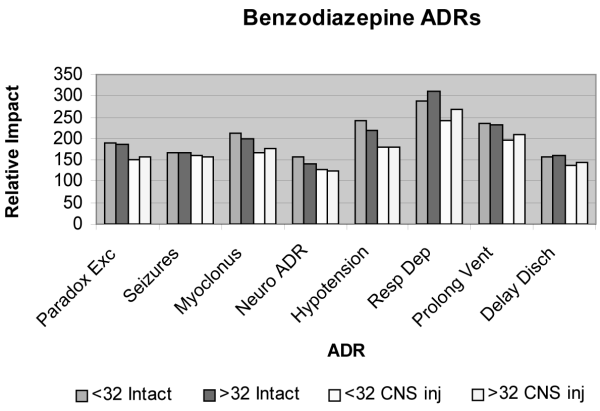
Background: Many infants are exposed to considerable pain as a result of disease processes, surgery or intensive care procedures. As a result babies are often exposed to prolonged treatment with drugs whose effects are unpredictable. This includes benzodiazepines, a class of drugs acting at GABAa receptors, which have been the subject of controversy [1]. In adult neurones, the effect of GABA is hyperpolarising (inhibitory), however it has been previously shown, *in vitro*, that in immature neurones GABA activity can result in depolarisation (excitation) [2]. Previous work in our lab has demonstrated this *in vivo*, by studying the responses of rat pups and mature animals to intrathecal administration of GABA, glycine and their antagonists. Here we have attempted to gauge the impact of this effect on clinical practice by the use of a questionnaire.

Methods: The British Association of Perinatal Medicine database was used to contact 400 neonatologists by post. The questionnaire was 'blinded' to its actual purpose by asking about the practitioner's experience of all the side effects of midazolam in neonatal practice listed in the Cochrane review of 2003. A relative impact was calculated as a function of the frequency of reporting and the severity of the reactions described.

Results: We found the reporting of 'parodoxical' neurological adverse events to be of significant magnitude (approaching 80% of the frequency of conventional ADRs overall in infants under 32 weeks with normal neurological development), myoclonus being the most prevalent.



Conclusion: The impact of previously unexplained, adverse, neurological events associated with benzodiazepine use in the very young is significant. It is likely that the mechanism of these effects may be explained in part by differences in GABAa receptor properties in the immature nervous system.

References:

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O6
A review of online, drug therapy clinical trial registers from a paediatric point of view

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Background: Access to ongoing clinical trial information is useful to anyone wishing to participate in trials and fundamental to those involved in health care for making knowledgeable decisions. Although many trial registers exist, accessing their data is not always easy or quick and users need to search numerous databases and cannot be sure of the results' completeness. Paediatric studies are more problematic than adult ones, so fewer exist. A review of freely accessible, online drug therapy registers was performed to determine how many include paediatric trial data, the therapeutic areas covered, quantity of information provided to users, and ease of use.

Methods: Medline and Google were searched to find existing registers. Only freely accessible, online registers involving multiple therapeutic areas/drugs and including ongoing trial data were included.

Results: Of 98 registers found, 79 were excluded, mainly cancer-oriented. 16 were completely accessible and 2 gave access only to trials whose eligibility criteria matched a user's personal information. Three (2 pharmaceutical company registers) provided limited data. Identifying paediatric trials was difficult. Most (17) registers included ≥1 paediatric study. The therapeutic areas covered by these paediatric trials were diverse, from cancer to infectious diseases. Only one register (www.dec-net.org) was exclusive to paediatric trials, but was still being established and therefore did not include all existing paediatric trials.

Conclusion: Many registers exist, but don't sufficiently facilitate users' searches for paediatric trials. Researchers seeking a complete view of ongoing studies must spend hours searching multiple registers with no guarantee that results are representative of reality.

O7
Efficacy of selective serotonin reuptake inhibitors (SSRIs) in treating depression in children and adolescents: an overview

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Background: Although the prescribing of antidepressants and other psychotropic drugs for children and adolescents is increasing, safety and efficacy of psychotropic drugs in the paediatric population are widely debated.

Methods: Medline, EMBASE and PsycINFO databases, company based clinical trial registries and drug regulatory agency websites were searched. Randomised controlled trials (RCTs) concerning the efficacy of antidepressants (venlafaxine and selective serotonin reuptake inhibitors [SSRIs]) in treating depression in children and adolescents were retrieved, and a systematic review concerning the improvement in symptoms of depression was performed.

Results: A total of 35 RCTs concerning antidepressant therapy for childhood depression were identified and 15 met the inclusion criteria, 6 of which were unpublished; 4 each concerned fluoxetine and paroxetine; 3 venlafaxine; 2 citalopram; and 1 each escitalopram and sertraline. From 1986-2004, 3154 patients aged 6-20 years were enrolled, and 73.5% completed the study. The studies lasted from 6 to 14 weeks (median 9 weeks). Wide differences were found in diagnostic and outcome measures, population size, and duration of treatment between studies. Pooled data from 8 trials showed a higher response rate with SSRIs (OR=1.68; 95%CI 1.31-2.14); however, a statistically significant difference compared to placebo was found only for fluoxetine and sertraline (OR=2.47; 95%CI 1.74-3.50 and OR=1.60; 95%CI 1.05-2.44, respectively).

Conclusions: While fluoxetine and sertraline seem to be effective in improving symptoms, more methodologically sound studies are needed to determine long term effects of SSRIs in children and adolescents.

O8
Pharmacogenetics in children: where does it "fit" into epilepsy treatment?

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Introduction: Epilepsy is a chronic disease in which patients are exposed to drugs for a long time. The current approach to anticonvulsant treatment is largely trial and error. There is a large proportion of children for whom medication is not safe or efficacious, and inter-individual variations in anticonvulsant drug response are among multiple reasons for this. Recent advances in genetic polymorphisms have contributed to understanding of variability in treatment efficacy and adverse effects. Can such pharmacogenetic information be applied to enable more rational and safe use of current anticonvulsant therapy?

Methods: Genetic polymorphisms can occur in genes for the drug target, drug transporter and drug metabolising enzymes. Polymorphisms in the cytochrome P450 (CYP) enzymes affecting drug metabolism have been best described to date.

Results: Which CYP to study? Variant alleles with known poor metabolism for enzymes involved in the metabolism of commonly used anticonvulsants are tabulated below. Pharmacogenetic information will be of most use if the prevalence of variant alleles is high and sufficient evidence exists to link variant allele to an altered clinical response to a drug.

Enzyme	Anticonvulsant substrates	Variant alleles with known poor metabolism	Prevalence of variant alleles (%)	Evidence for altered clinical response
CYP1A2	Carbamazepine, ?Phenytoin	CYP1A2*1C	Unknown	Weak
CYP3A4	Carbamazepine	Not known	–	–
CYP2C8	Carbamazepine	CYP2C8*2 CYP2C8*3 CYP2C8*4	18 (Af),? (C) 13 (C), 2 (Af) 7.5 (C)	Significantly defective metabolism of paclitaxel and arachidonic acid
CYP2C9	Phenytoin, Phenobarbitone, Valproic acid	CYP2C9*2 CYP2C9*3 CYP2C9*5	20 (C) 10 (C) ?	↓ dose requirement ; ↑ adverse effects in phenytoin
CYP2C19	Phenytoin, Phenobarbitone, Valproic acid	CYP2C19*2A CYP2C19*3A CYP2C19*4	13 (C),30(As) 0.3 (C),5(A) 0.6 (C)	Decreased metabolism of omeprazole and phenytoin,

C=Caucasian, Af= African-American, As=Asian

Conclusion: From the above information we have identified CYP2C8, CYP2C9 and CYP2C19 as potentially useful candidates for pharmacogenetic study in anticonvulsants. Large clinical trials are needed to define whether there is sufficient evidence to proceed with prospective genotyping to aid anticonvulsant choice and dosing regime.

O9
Management of paediatric clinical research in a changing environment: infrastructure and organisation requirement

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Background: The benefits of performing paediatric clinical trials in academia are numerous, although they present many challenges. This session will focus on the initiation of clinical research and the infrastructure needed to manage the practical and administrative aspects from development to data analysis.

Methods: The Paediatric Clinical Research programme at Yale has a support structure which enables high quality clinical investigation to be completed efficiently and in a cost effective manner. The support team is composed of staff at multiple skill levels. This structure allows the researcher to focus solely on science while providing the infrastructure for data collection and regulatory management. The department has access to dedicated outpatient/inpatient research space including offices, storage, exam and laboratory space.

Results: This structure allows for a rapid initiation process, efficient recruitment, and financially responsible management. The department's grant activity has grown substantially since implementing this structure and more faculty members have participated in clinical research projects, both industry sponsored and investigator-initiated activities. Having trained staff has allowed for the development of a network of community clinics and private practices to enable recruitment.

Conclusion: The structure has allowed junior faculty to participate and develop ideas in a structure that provides support for all activities and a network of patients to recruit from. The Yale University Paediatric Department support model is now serving as a model for the entire School of Medicine. Although central support models for research are common, such models are less common in the specialties of paediatric medicine.

O10
Predicting pharmacokinetics in children using PK-Sim

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Background: Approaches that are able to predict potential differences in the pharmacokinetic behaviour of a compound in children compared to adults are highly desirable for clinical trial preparation in terms of dosage adjustments, therapeutic response analysis and risk assessment. Physiology-based pharmacokinetic (PBPK) modelling allows for the simulation of concentration-time profiles in plasma and other organs based on a combination of physiological and substance specific parameters. PK-Sim (Bayer Technology Services, Leverkusen, Germany) is a software tool designed to account for age dependent physiology, which are critical elements for PK prediction in children[1]. Clearance prediction in children was also completed in PK-Sim and based on the physiological maturity and enzymatic ontogeny of the responsible elimination processes[2,3]. The objective of this study was to determine the appropriateness of PK-Sim and its clearance prediction module to correctly predict plasma concentration-time curves of model compounds such as morphine and levofloxacin.

Methods: Experimental plasma concentration-time data following intravenous administration was gathered from the literature for various age groups. Predictions were generated in PK-Sim for each literature study using the mean age and weight of the subjects, as reported. Additional input information consisted of the physio-chemical properties of the compound as well as the administration regime.

Results: Trends associated with the differing age groups as well as experimental plasma concentration-time curves were extremely well represented by PK-Sim predictions. Preterm and term neonates had greater plasma concentrations in comparison to children 6 months of age and older. Children greater than 6 months had lower plasma concentrations in comparison to adults. This is a result of both the age-dependence of clearance and disposition.

Conclusion: PK-Sim and clearance scaling are very well suited for the prediction of plasma concentration-time data in children. This approach will not only aid in paediatric clinical trial development but has the potential to reduce the number of required patients.

References:

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