European Society for Developmental, Perinatal and Paediatric Pharmacology, 10th Congress

The 10th Congress was held in Stockholm, Sweden on 14–17 June 2006. The President for the meeting was Anders Rane. The Congress discussed advances in neonatal therapy, the proposed legislation in the European Union, pharmacoepidemiology of drugs in pregnancy and psychotropic drug use in children. Other topics covered included the use of anabolic steroids in teenagers, immunotherapy for paediatric rheumatic disorders, drug therapy in pregnancy and the developing fetus and the treatment of urea cycle defects.

There was a special tribute to Lars Boréus (President of the ESDP 1990–1992) who passed away in December 2005. He had been a pioneer in paediatric clinical pharmacology in Europe. Commemorative words were given by the President Anders Rane, Kalle Hoppu from Finland and Sumner Yaffe from the USA. In memory of Lars Boréus, the Society decided to award the Lars Boréus Prize to the best oral free communication from a young investigator. The first Lars Boréus Prize was awarded to Miklós Szabó from Budapest, Hungary for his presentation on 'The possibility of altered pharmacokinetics of morphine in neonates treated with prolonged hypothermia'. The prize includes free registration and accommodation at the next ESDP Congress, which will be held in Rotterdam in June 2008.

There were 12 oral free communications (O), 19 mini-oral presentations (M) and 29 poster presentations (P). The abstracts for 19 of the invited lectures are also shown below (L).

L1
Clinical trials of surfactants: developing a protocol to guide therapy of respiratory distress syndrome

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Background: Respiratory distress syndrome (RDS) was shown to be caused by surfactant deficiency in 1959. The first report of successful surfactant therapy was in 1980 when 10 preterm infants with RDS were treated with a bovine surfactant. Since then there have been many randomised controlled trials (RCTs) aimed at assessing efficacy, timing, number of doses, methods of administration, types of surfactant and other aspects of surfactant therapy.

Aim: To review the results of these RCTs and systematic reviews so that an evidence-based protocol for surfactant treatment may be developed.

Methods: RCTs and systematic reviews of surfactant therapy were sought in PubMed and the Cochrane Library. Relative risks (RR) and numbers needed to treat (NNT) together with their 95% confidence intervals (CI) were calculated for various outcomes.

Results: Natural (animal-derived) and synthetic (protein-free) surfactants both reduce the risks of pulmonary air leaks and neonatal mortality when used either as prophylaxis (within 10–15 min of birth) or as rescue treatment for RDS. Comparison trials show that natural surfactants are more effective than synthetic surfactants at reducing air leaks and mortality. RCTs also show that multiple doses (up to three) are better than single doses for infants who relapse. For infants < 31 w gestation, prophylaxis is better than rescue as regards survival, severe intraventricular haemorrhage and chronic lung disease (CLD). The natural surfactants are not equivalent and a meta-analysis of five RCTs comparing poractant (porcine) and beractant (bovine) in rescue studies shows that the former acts more rapidly. When poractant (dose 200 mg/kg) is compared to beractant (100 mg/kg) there is reduced neonatal mortality (RR 0.29; 95%CI 0.10 to 0.79; NNT 14; 8 to 50). Comparative prophylaxis trials with these surfactants have not been performed. For prophylaxis, treatment before RDS has developed, 100 mg/kg may be sufficient as surfactant inactivation is unlikely. Surfactant and CPAP together have been shown to be effective in reducing the duration of and need for mechanical ventilation and should therefore reduce CLD but this needs to be proved. Trials of new generation synthetic surfactants containing analogues of SP-B or SP-C have recently been published but there is no convincing evidence that they are better than the existing natural surfactants. However, they may have a role in ARDS where surfactant inactivation is likely.

Conclusions: An evidence-based protocol for surfactant therapy should be based upon prophylaxis for infants < 27 or 28 w; early rescue for others and trials of CPAP wherever possible. Natural surfactants are better than the currently available synthetic preparations and poractant may have advantages over beractant although this may be dose-related. The role of the new generation synthetic surfactants remains to be determined.

L2
New applications of therapy with inhaled nitric oxide (NO)

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Nitric oxide (NO) is a gas at room temperature and for several decades has been recognised as an urban air pollutant that is generated during combustion. Furthermore NO is unstable in air and spontaneously forms higher oxides of nitrogen, mainly nitrogen dioxide. In the late 1980s it became clear that most cells have the ability to enzymatically generate minute amounts of NO from the amino acid L-arginine and molecular oxygen. In target cells, NO can have a variety of effects. NO may also bind to sulphur-containing proteins and nitrosylate thiols.

Inhaled NO (iNO) is a selective pulmonary vasodilator. Since 1999 (USA) and 2001 (EU) iNO is a drug with

marketing authorisation for the indication hypoxic respiratory failure of the newborn[1]. The documented doses for the approved clinical application are in the parts per million (ppm) range, with a maximum recommended dose of 20 ppm continuously delivered for a period of up to a few days. Special delivery systems and continuous monitoring of inhaled gas concentrations are required for safe clinical use. iNO is also currently used clinically in an off-label manner with the main aims of producing improved oxygenation and reduced lung vascular constriction[2]. At present, several randomised multicentre studies are under way, examining other potential indications for this therapy. More recent experimental data suggest that higher doses of iNO also may have extrapulmonary pharmacodynamic effects. Among them we can note modifications of renal function and immunological responses to a challenge with endotoxin[3].

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Disclosure: Author CF has financial interest in the clinical use of iNO, and has acted as a consultant to industry.

L3
Pharmacological treatment of neonatal encephalopathies

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Brain protection of the newborn remains a challenging priority for the next future. Perinatal brain damages have different anatomical localisations as a function of gestational age secondary to different sensitivity of white and grey matters at different steps of brain development (i.e. preterm and at term newborns). In term newborns, cortical and brainstem injuries after an hypoxic-ischaemic event are an evolving process with a primary cell death and a secondary continued neuronal and oligodendroglial injury during several days or possibly weeks after initial insult. The clinical presentation of precocious neonatal encephalopathy is of variable severity (grade I to III). Conversely, in preterm newborns, white matter injuries and secondary grey matter developmental alterations have more often no clinical expression during the first weeks of life and are at best diagnosed by cerebral ultrasonographic or MRI studies. These conditions in term and preterm newborns are associated with high neonatal mortality and severe long-term neurological morbidities.

Whatever the term and the localisation of brain injuries, it seems that their aetiology is of multifactorial origin involving (i) preconceptional maternal factors such as genetic polymorphisms, nutritional deficiency or exposure to toxic agents, (ii) perinatal factors such as chorioamnionitis and other inflammatory factors incurring increased production of cytokines, perfusion failure/hypoxia incurring increased production of free radicals and excitotoxins, maternal and/or placental hormonal and growth factor deficiency due to early interruption of pregnancy, post-natal hypoxia or severe hypocapnia, nutritional deficiency, or side-effects of postnatal treatment of neonates.

Several potential neuroprotective strategies could be proposed. These strategies are hard to apply to human newborns due to the difficulty in knowing when the triggering event leading to the deleterious cascade is occurring and due to the side effects of a lot of potential protective molecules. However, we hope to decrease the delayed phase of brain injuries with some protective molecules with minimal side-effects.

In term newborns, no pharmacological therapies other than supportive measures for neonatal encephalopathies can be proposed. A non-pharmacological technique, hypothermia has been shown to have short-term benefits on mortality and disabling cerebral palsy up to 18 months of age when used under strict protocols in term newborns. Its optimal use, the long-term benefits in neurodevelopmental outcomes and the long-term safety remain to be established. In the future, some molecules such as minocycline, corticosteroids, inhibitor of xanthine oxidase or erythropoietin may find a place in the treatment of encephalopathies of term newborns but their protective effects have to be demonstrated in specific trials[1,2].

In preterm newborns, antenatal corticosteroid therapy has been shown to decrease the rate of white matter injuries but their effect on long-term disabilities remains to be confirmed. In a recent study[3], repeated antenatal courses of corticosteroids may protect against cerebral palsy but are associated with hyperactivity later in childhood. In the EPIPAGE study, a population-based cohort study of preterm infants born in nine regions of France in 1997 and followed until five years of age, antenatal corticosteroid therapy had no significant effect on the occurrence of cerebral palsy (unpublished results). The use of antibiotics following preterm rupture of membranes is associated with reduced abnormal cerebral ultrasound scan prior to discharge from hospital[4].

In several human observational studies, prenatal administration of magnesium sulphate was reported to be associated with lower mortality and lower risk of cerebral palsy. Three randomised trials were undertaken in recent years using magnesium sulphate to protect the brain. An Australasian study showed a significantly lower rate of substantial gross motor dysfunction at two years of age[5]. In the French Premag trial, total mortality, severe white matter injury and their combined outcome were less frequent in the magnesium sulphate group but the differences did not reach statistical significance[6].

Indomethacin has been used with success in the prevention of parenchymal haematoma and has no deleterious effect on the occurrence of cerebral palsy at three years of age[7]. Nitric oxide and erythropoietin could be interesting in the future but their protective effect must be proved in pilot trials[8,9].

A "cocktail" combining several molecules acting at different points of the deleterious cascade leading to brain injury should be better than only one molecule acting at a single point. Neonatologists anxious to propose new trials to protect the developing brain need to be aware of this.

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L4
Perinatal brain damage: immuno-inflammatory mechanism

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Subclinical infections during pregnancy may be an important aetiological factor of brain injury and subsequent neurological sequelae. Chorioamnionitis, or positive cultures and elevated interleukin-6 (IL-6) in the amniotic fluid of pregnant women with preterm contractions increase the likelihood of preterm birth and subsequent white matter injury. Furthermore, the risk of brain injury appears to be higher in cases of preterm birth with spontaneous onset (often infection-related) than in physician-initiated (often not infection-related) cases. We recently found that histological chorioamnionitis, clinical chorioamnionitis and fever during pregnancy were associated with the occurrence of cerebral palsy (CP) and this relationship was stronger for infants born preterm <32 than 32 – 36 w. Other studies indicate, however, a strong relationship between antenatal infection and cerebral palsy in term infants. Some cytokine/chemokine levels in the blood of the newborn are much higher in those cases that subsequently develop CP as compared to non-CP controls.

Antenatal infections also seem to increase the risk of birth asphyxia. In addition, the combination of infection and birth asphyxia is strongly associated with CP and the association is much stronger than either factor alone suggesting a synergistic effect. Experimental studies suggest that a low dose of bacterial endotoxin, administered to newborn rats, dramatically sensitises the brain to hypoxia-ischaemia (HI). We found an up-regulation of mRNA for CD14 and the presence of TOLL-like receptor 4 in the brain, suggesting that the innate immune system may determine the vulnerability of immature brain.

Inflammation is induced in the immature brain also in response to sterile insults like HI which may appear counterproductive. The ultimate objective from an evolutionary perspective is most likely to eliminate microbes and limit their dissemination (at the cost of local tissue injury) until proven that the insult is of non-infectious origin. We believe that microglia constitute the main sentinel immune cell of the immature CNS and there are data to suggest that these cells aggravate injury during the early recovery phase after HI: (a) microglia activation occurs within the time frame of injury development ; (b) several CC-chemokines (that activate microglia) are expressed after HI and neutralisation of these reduces injury;(c) microglia seems to be the main producer of interleukin (IL)-1, TNF-, IL-18 and NO that all seem to contribute to the development of brain injury; (d) poly(ADP-ribose)polymerase (PARP) is important for macrophage/microglia migration and activation, and PARP inhibitors are protective and PARP deficiency confers protection.

Even though some data suggest the involvement of PMNs, very little information is available with regard to the involvement of other immune cells (eosinophils, mast cells, dendritic cells, T-, B- and NK cells) and the immunomolecules involved in their regulation are still largely unknown. Novel microarray data will be presented on global gene induction after HI which offers some clues with regard to the proteins that may participate in the inflammatory process.

It is still uncertain how the pro-inflammatory response induces oligodendroglial and neuronal cell death. There are data in support of both a death receptor pathway leading to activation of caspase-8 dependent apoptotic cell death and a RIP-dependent necroptosis blocked by necrostatin-1. We suggest also that a MAP-kinase dependent pathway leading to JNK3 activation, mitochondrial outer membrane permeabilisation and cell death is critical.

In conclusion, clinical and experimental studies suggest that infection and cytokine-mediated inflammation play a role in the process leading to brain damage in term and preterm infants.

L5
European regulation

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The EU Commission presented its proposal for a EU Paediatric Regulation on 29 September 2004. The objective of the regulation is to improve the health of the children of Europe by increasing high quality research into medicines for them, promote the development and authorisation of such medicines, and improving the information on medicines designed for children, while avoiding unnecessary studies in children and not delaying the authorisation of medicines for adults. Key measures of the regulation are a requirement for paediatric data based on an approved Paediatric Investigation Plan (PIP) to be presented at the time of application for marketing authorisation for all new medicinal products, and for authorised medicinal products covered by a patent or a supplementary protection certificate (SPC). This has to be done in order to obtain validation of a marketing authorisation application or an application for a new indication, new pharmaceutical form or new route of administration, unless a waiver or a deferral has been granted. The combined reward and incentive, if all the measures included in the agreed paediatric investigation plan are complied with, if the product is authorised, when appropriate, in all Member States and if relevant information on the results of studies is included in product information, is a six-month SPC extension. A Paediatric Committee responsible for the assessment and agreement of paediatric investigation plans and requests for waivers and deferrals will be established at the EMEA. To provide incentives for off-patent medicines, a new Paediatric Use Marketing Authorisation (PUMA) for medicinal products developed exclusively for use in children is established. It will give 10 years of data protection to the paediatric development, based on an agreed PIP, of an off-patent medicine. Special funding for studies into the paediatric use of medicines not covered by a patent is planned. In addition, measures to increase the information available on the use of medicines for children, and building the current Community database of clinical trials (EudraCT) to an information resource of all ongoing and terminated paediatric studies conducted both in the Community and in third countries are included. The Regulation also proposes to create a Community network to link together national networks and clinical trial centres in order to build up the necessary competences at a European level and to facilitate the conduct of studies, to increase co-operation and avoid duplication of studies. The Regulation is now in the final stages of adoption in the EU Parliament and is expected to come in force later this year. The EU Commission documents are available from: http://ec.europa.eu/enterprise/pharmaceuticals/paediatrics/index.htm.

L6
Predictive value of juvenile animal studies

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Although the use of juvenile animal studies to support the safe testing of pharmaceuticals in humans is not new, recent "shifts" (notably in the US) requiring the more widespread need for paediatric clinical trials has led to increased interest in these non-clinical studies. It is well established that adverse events in children may not be predicted from adult experience and by extension of this observation, juvenile animal studies may identify toxicological signals not seen in young adult animals (a point covered in recent regulatory guidance documents from the US and Europe). However, we are still at a stage of identifying what "unique toxicities" may occur in juveniles which could result in production of unnecessary and uninterpretable data. This presentation will comment on the available guidance in this field as well as general considerations associated with juvenile animal testing itself before addressing the predictive value of (and concerns associated with) such testing and what the future may hold.

L7
Dose finding studies in children

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The medical care of the children of Europe is facing a drastic change. With the new regulation on medicinal products for the paediatric use coming into effect during the next year, the patients, physicians and pharmacists will encounter a new class of pharmaceuticals. A special label showing a large, blue "P" in front of the silhouette of a star will draw attention to drugs specifically approved for children. But the valuable lesson from the US legislation shows that although a quantum leap in applications for children's drugs was registered, about 40% of the applications did not succeed; the main reasons being lack of efficacy or unwanted side effects of the drugs. As under- or overdose are not uncommon in children due to the ontogeny of pharmacokinetics and pharmacodynamics, age appropriate dosing might be crucial for a successful application. Therefore, dose finding strategies need to be implemented into the study design. To approach this problem and to build a rationale for trials in worthwhile drugs, we evaluated the prevalence of dosing errors in paediatric patients from the paediatric cardiology and respiratory unit of the Children's Hospital of the University of Düsseldorf. All drug orders were evaluated in patients over the period of two months. The dose was judged on the background of the actual German Fachinformation and the new British National Formulary for Children (BNF 2005). Errors were defined as a drug over- or under-dose or off-label use. In total, 151 patients (51% male, 49% female, median age 1.8 years) were investigated. The analysis revealed that 51% of patients had dosing errors. Of those 18.4% were over-dosed, 11.2% were under-dosed and 21.4% were treated off-label. The high prevalence (51%) of uncertainty in dosing confirms that dose finding strategies should be implemented into the study design of paediatric clinical trials. In the presentation examples of such strategies will be discussed.

L8
What industry-driven paediatric research on patent-protected and off-patent drugs will be stimulated by the EU regulation?

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US Pediatric Exclusivity (PE) has, since 1997, triggered research on many patent-protected modern drugs. These have a comparable role in pharmaceutical treatment in Europe. Today, most modern drugs have data on PK/PD, dosing in younger age groups, and on safety and efficacy or at least activity in the same indication as in adults. In some cases where the adult disease does not exist in children, different conditions were investigated in children, e.g. bisphosphonates in osteogenesis imperfecta, or tamoxifen in McCune-Albright syndrome. The mandatory path of the US legislation PREA (Pediatric Research Equity Act) 2003 has led to the inclusion of paediatric aspects into the general drug development process. For drugs with FDA-triggered paediatric data a genuine European contribution will need new research targets, e.g. additional age groups, sub-populations, or new indications, including rare diseases. Industry will be interested to pursue this second wave of paediatric research in exchange for six months protection against generic copying. As this reward is linked to an existing patent and many drugs' patent will expire soon, the result of the EU Paediatric Regulation will depend on the speed and dedication of EMEA and the future Paediatric Committee (PC). The PC does not yet exist but companies are currently in need of a dialogue partner on what paediatric research will be sufficient for the 6 months protection reward. The SAWG (Scientific Advice Working Group) could play a key role during the transition phase. The further away patent expiry is, the more the EMEA PC will be consulted on paediatrics in earlier drug development stages.

PUMA (Paediatric Use Marketing Authorisation) offers 10 years data exclusivity for off-patent drugs. Large companies usually stop clinical research in projects they can no longer defend against generic copying. PUMA might be considered for some patent protected drugs during the period preceding patent expiry. A PUMA protection might allow a large company to defend at least a part of the established brand. For older products PUMA might attract small and medium-sized companies, provided they can calculate the return of investment made for initial financing of paediatric research projects. For both scenarios, the draft paediatric regulation will need to be supplemented by PUMA implementation rules and a supporting national framework: will a PUMA licence be granted to the first company that declares its intent to perform a paediatric research programme, to the one that starts such a programme, or to the one that submits data? Can a generic company request a later PUMA licence before patent expiry? Will National Health Authorities and insurers prevent substitution of higher priced PUMA products by cheaper generics?

Old off-patent drugs will probably not attract investments from pharmaceutical companies. Here, the Paediatric Research Grant Programme announced by the EU Commission 2004 will probably play a key role. Announced as MICE (Medicines Investigation for the Children of Europe), a new name is now being considered by the Commission. Its impact will depend on the assigned budget.

The debate about an EU paediatric regulation has contributed to further remove mental barriers against paediatric research. To make it work, implementation rules will be needed as well as effective communication between regulators, pharmaceutical industry, clinicians and other key stakeholders. The dialogue between these partners in health care needs to be strengthened.

L9
Advantages and possibilities in using register-based prescription data – the Finnish experience

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In Finland, the existence of several nationwide registers offers a valuable opportunity to perform epidemiological studies. The Social Insurance Institution of Finland (KELA) maintains a national Prescription Register, comprising all purchases of medicines which have been reimbursed immediately upon purchase, and covering 97% of all reimbursed prescriptions. Prescription-only medicines deemed necessary for the treatment of an illness are reimbursed under the Health Insurance Scheme. Some over-the-counter (OTC) drugs are also reimbursable when prescribed by a physician. In addition to the information relating to the patient, the prescribing doctor, and the date of purchase, the Prescription Register includes detailed information on the medicine (categorised according to the Anatomical Therapeutic Chemical classification, ATC), and on the cost and reimbursement paid for the medicine. The register also contains a special code for specially refunded drug purchases. Patients with specified chronic diseases (about 50 diseases in total) are entitled to special refunds for drug treatment costs. Every person entitled to special refunds is recorded in the Special Refund Register.

The unique personal identification number assigned to each citizen at birth enables the use of register data for research purposes. Prescription Register data have been utilised in pharmacoepidemiologic studies investigating drug use in particular age cohorts, and the incidence and drug costs - including costs related to comorbidity - of certain chronic diseases requiring drug treatment. Linking Prescription Register data to data derived from other nation-wide registers offers several possibilities for research. One such example is the continuing surveillance system "*Medicines and Pregnancy*", established by three governmental organisations (KELA, the National Research and Development Centre for Welfare and Health STAKES, and the Finnish National Agency of Medicines). The purpose of the project is to assess the effects of prenatal drug exposure on the outcome of pregnancy, including major malformations. Accordingly, Prescription Register data have been linked to data derived from the Medical Birth Register, the National Register of Congenital Malformations and the National Register of Induced Abortions, all maintained by STAKES. Several sources of limitations encountered in studies based

on interviews can be avoided by using population-based register data. The advantages and possibilities, as well as the shortcomings in using register data will be discussed in context of the "*Medicines and Pregnancy*" project.

L10
Building an international antiepileptic drugs and pregnancy register when national databases are insufficient

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Background: Use of antiepileptic drugs (AEDs) during pregnancy is associated with a 2-3 fold increased risk for birth defects in the offspring. These adverse effects of AEDs need to weighed against the fetal and maternal risks with uncontrolled seizures, and most women with epilepsy will require treatment during pregnancy. Unfortunately, information on the comparative teratogenicity of AEDs is conflicting, preventing a rational approach to AED treatment in women of childbearing potential. This is mainly due to inadequate sample size of studies completed to date. Major collaborative efforts are necessary to provide sufficient data for a condition that accounts for less than 0.5% of all pregnancies and for which at least 15 different drugs are available. Based on these considerations, a multinational registry has been established aimed at determining the comparative risk of major malformations following intake of AEDs during pregnancy.

Method: EURAP is a prospective registry set up originally in Europe and later extended to 40 countries in Asia, Oceania and South America. Women taking AEDs at conception are enrolled in early pregnancy before fetal outcome is known. Information on potential risk factors is obtained, and follow-up data collected online each trimester, at birth and at one year after delivery. Feedback between the central registry and reporting physicians allows collection of missing data. A committee that is unaware of the type of drug exposure classifies fetal outcome.

Results: By March 2006, more than 8,000 pregnancies have been enrolled and close to 4,000 completed one-year follow-up after birth.

Conclusion: Intensive on-line interaction between the central registry, regional coordinators and reporting physicians has proven an effective means of ensuring efficient enrolment and follow-up on an international basis.

L11
Use of psychotropic medications in Italian children and adolescents

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Background: Although the evidence of psychotropic drug safety and efficacy in the paediatric population is scant and widely debated, their prescription prevalence is increasing. A drug utilisation study based on a multiregional prescription database (ARNO) was therefore performed to evaluate the use of psychotropic drugs in children and adolescents in Italy.

Methods: The psychotropic drug prescription prevalence was estimated in a sample of 1,484,384 children <18 years old during 2004. Furthermore, the trend of psychotropic prescription prevalence was evaluated from 1998 to 2004.

Results: During 2004, 4316 children < 18 years old received psychotropic drugs (2.91/1000 youths). Antidepressants were prescribed to 3503 youths (2.36%), antipsychotics to 1005 (0.68%), and lithium to 73 (0.1%). The prevalence rate of psychotropic drug prescriptions increased with increasing age, with a statistically significant trend (χ^2_t = 2443; P<0.0001).

The psychotropic prescription prevalence increased in the period 1998-2004 with a statistically significant trend (χ^2_t = 298; P<0.0001), reaching its highest value in 2002 (3.08%). The antidepressant trend was similar to the overall trend, while the prevalence of antipsychotics did not increase.

Conclusions: Even if the prevalence of psychotropic drug prescriptions in Italian children is lower than that reported in other countries (e.g. United States, Canada, Netherlands, UK), the increase in SSRI prescriptions raises some concerns. Data concerning effectiveness and safety of these antidepressants in paediatrics are still limited and further studies are needed to guarantee safe and effective evidence based therapeutic approaches in children, adolescents and their families.

L12
Epidemiology of psychotropic drugs in UK

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Background: Due to different economic, ethical and technical reasons, paediatric psychotropic medicines research is poorly developed. A large number of psychotropic drugs are not licensed for use in children and adolescents due to lack of research.

Methods: We used large databases (General Practice Research Database and IMS MediPlus Database) to study the prescribing of paediatric psychotropic drugs in the UK.

Results:

1) The prevalence of prescribing of ADHD treatment increased between 2001 and 2005. Prevalence increased 3.1-fold in females (from 0.27 per 1000 patient-years in 2001 to 0.83 per 1000 in 2005) and 2.8-fold in males (from 1.91 per 1000 patient-years in 2001 to 5.38 per 1000 in 2005).
2) The prescribing of CSM-withdrawn antidepressants for depression rose from 2000 to 2002 (1.2 to 1.6 per 1000 patient, P<0.001), but dropped between 2002 and 2004 (1.6 to 1.0 per 1000 patients, P<0.01).
3) There was a two-fold decline in the prevalence of typical antipsychotic prescribing in 2000 compared to 2004 (0.46 to 0.20 per 1000 patient-years), where as there was an almost 3 fold increase in the prevalence of atypical antipsychotic prescribing from 2000 to 2004 (0.19 to 0.55 per 1000 patient-years).

Conclusion: ADHD treatments and atypical antipsychotics prescribing have increased significantly in recent years. Although, the CSM warning reversed the increasing trend of SSRIs and related antidepressants prescribing, there are still a significant number of children and adolescents taking such antidepressants. The use of psychotropic drugs in children and adolescents is no longer a rare event.

L13
Doping in teenagers

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Background: Anabolic-androgenic steroids (AAS) are widely abused among young men wishing to improve their physical appearance. AAS have performance-enhancing effects, speed recovery and induce muscle growth, but also possess potent psychoactive and endocrine properties. This leads to undesired psychiatric, endocrine and physical effects, particularly in adolescents believed to be highly susceptible to the effects of AAS.

Methods: Psychiatric characteristics, behavioural changes, endogenous endocrine functioning and adverse physical effects following abuse of AAS were monitored in a group of young men. Informed consent and approval from the Clinical Research Ethics Committee was obtained. A recent abuse of AAS was confirmed by urine analysis. For diagnosing psychiatric conditions, individuals underwent "Structured Clinical Interview for Diagnosis 1+2" (SCID). Endocrine functioning was measured following standard hospital procedures. Detailed and structured somatic examinations were repeatedly performed upon all individuals.

Results: SCID-interviews revealed an over-representation of personality disorders and affective disorders in the study group. Furthermore, AAS suppressed endogenous

endocrine functioning as shown by a robust and time dependent suppression of not only LH and FSH, but also of testosterone. Somatic examinations revealed cases of gynaecomastia, testicular atrophy, severe acne, striae and accelerated balding.

Conclusion: AAS abuse in adolescents results in impairment of the endogenous endocrine functioning, leads to increased affective instability and results in various undesired somatic effects described above.

L14
Overview of new therapeutic principles in paediatric rheumatic diseases

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The therapeutic management of childhood rheumatic diseases has considerably changed during the last decade. This is due to a better knowledge of the "classical" therapies and minimising toxicity. But most progress has been due to the development of new molecules targeted to specific immunological anomalies.

Corticosteroids (CTS) are necessary for many children with inflammatory or auto immune diseases. Many well known side effects cannot be avoided. Several studies are now available indicating the interest of GH. In most cases, GH restores normal growth velocity without catching up. Early GH therapy introduction in children in whom CTS seems necessary for a long time might improve final height. Osteoporosis may be reduced by the use of bisphophonates.

More recent non specific therapies have been developed. Leflunomide (Arava®) may be an alternative to Methotrexate. Thalidomide seems to improve systemic JIA, with an interesting CTS sparing effect. The tolerance is generally acceptable. Autologous stem cell transplantation (ASCT) has been used with about 50% complete remission without therapy. But the high rate of fatalities with this procedure means that ASCT is only indicated in exceptional circumstances. Furthermore, the possibility of using new molecules with more specific targets will transform the therapeutic landscape in the very near future.

"Biologics" with a molecular target. These molecules aim at reducing the levels of harmful cytokines such as TNF, IL1 by using either their natural inhibitors or specific antibodies. IL6 complexed in vivo with its receptor can be inhibited by neutralising IL6R. Increased B cell activity can be reduced with anti B cell antibodies.

A very new strategy is now emerging by controlling co-stimulation between naive T cell activation and antigen presenting cells. CTAL-4Ig (Abatacept) which interacts with the co-stimulating signal has been used in PR with very encouraging results. The first results obtained with this molecule in JIA show a high rate of improvement with a good tolerance.

L15
Anti-TNF therapy (etanercept) for juvenile rheumatic disorders

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Background: Tumour necrosis factor (TNF) has been shown to be related to the inflammatory process in a number of juvenile rheumatic disorders (JRDs) e.g. JIA, JIA associated uveitis and dermatomyositis (JDM). Etanercept (E) is a dimeric fusion protein of the human extracellular p75 TNF receptor linked to human Fc IgG1. E is the most widely used and most extensively studied of the anti-TNF biologics in children with JRDs.

Methods: This presentation will provide an overview of the published randomised clinical trial (RCT) and open label studies in Poly JIA, safety data from a large North American registry and recent data describing induction of "inactive disease" and "clinical remission on medication" in Poly JIA. In addition, open label studies of E in systemic JIA and JIA associated uveitis will be reviewed.

Results: In a double-blind, placebo controlled RCT in 69 children with JIA with active polyarticular manifestations, 74% demonstrated an ACR Paediatric 30 response after 3 months of open label E 0.4 mg/kg twice weekly subcutaneous and significantly fewer flares compared to placebo (28% vs 81%, respectively, $P< 0.001$). Recent analyses of ≥4 years of follow up in these same subjects demonstrate continued clinical benefit. In a registry of Systemic and Polyarticular JIA subjects on either methotrexate (n = 198, 386 patient years of exposure) or E (n = 403, 680 years of patient exposure), 21% vs 20% reported an adverse event (AE), 6% vs 7% a severe AE, 17% vs 12% insufficient therapeutic response, 11% vs 4% remission and discontinuation due to AE 1.5% vs 0.5%, respectively. Open label experience in systemic JIA and JIA associated uveitis demonstrated obvious clinical benefit in > 50% of the subjects.

Conclusion: E has a clearly established role in the treatment of Polyarticular JIA with an excellent risk/benefit balance. The role in Systemic JIA and JIA associated uveitis is promising but not established by RCT experience.

L16
Some new biologic therapies for paediatric rheumatic diseases

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This talk will concentrate on 3 biological therapies: tocilimumab, anakinra, and rituximab.

Tocilimumab is a humanised antibody to the IL-6 receptor, thus blocking the IL-6 signal. IL-6 is a key cytokine that recruits inflammatory cells to the site of inflammation via its action on chemokines and adhesion molecules. It also induces inflammatory cytokine antagonists such as soluble TNF receptors and IL-1 receptor antagonist (IL-RA). Its level is very high in the serum of systemic juvenile idiopathic arthritis (sJIA) and the rationale and results of a phase II study of Tocilimumab will be presented.

Anakinra is a recombinant protein that acts similarly to the natural IL-1RA and so it is the rational drug to block excessive IL-1 production found in some of the systemic paediatric diseases such as familial autoinflammatory syndromes. It has also efficacy against RA, and some sJIA patients. The problem is its short half life, and injection reactions. Our local experience will be presented in the context of the NIH trial and also reports from other centres.

Rituximab (anti CD20) depletes pre B and mature B cells and has been useful in lymphoma treatment. More recently anecdotal reports suggest that it is a well tolerated method of treatment for antibody producing diseases such as RA, SLE and some vasculitides.

L17
Fetoscopic surgery takes its place in modern fetal medicine

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Today, fetoscopy has gained clinical acceptance in fetal medicine and perinatalogists should be familiar with its indications and perinatal problems. Obstetrical endoscopy includes surgery on the placenta, umbilical cord and fetal membranes. The most common procedure today is laser coagulation of anastomoses for feto-fetal transfusion syndrome (FFTS). A recent RCT by the Eurofoetus group[1] demonstrated that laser is superior to amniodrainage, improving both survival and neurological morbidity in survivors. Therefore patients should be offered this intervention as a primary therapy once the diagnosis is made. Longer term follow up studies have confirmed improved morbidity, the absence of renal problems in donors, and a higher risk for right ventricular outlet tract obstructions in recipients. Furthermore, the pathophysiology is increas-

ingly understood, and other complications of monochorionic pregnancies are being considered for fetoscopi "bochorionisation. Fetoscopy is also used to occlude the cord of a non-viable twin in monochorionic multiplets, and long term follow up studies have shown an overall survival rate of >85% with neurological morbidity restricted to live born babies prior to 28 weeks, after iPPROM. For all these procedures, the effect of a learning curve has been demonstrated. For the above operations, we have shown that maternal remifentanyl administration decreases fetal movements during the procedure.

Fetoscopy is now also used for in utero fetal *surgery*. It is used to occlude the fetal trachea for severe congenital diaphragmatic hernia, i.e. in the fetus with lethal pulmonary hypoplasia. Fetuses with isolated CDH, liver herniation and a lung-to-head ratio <1.0 are operated between 26 and 28 weeks and the balloon is removed at 34 weeks, followed by optimal neonatal care. This procedure has improved outcome by 50%. Usually the latter procedure is done under loco-regional anaesthesia, with fetal immobilisation and fentanyl. At this moment randomised trials are being set up to evaluate the value of fetal therapy in these conditions. For all procedures maternal invasiveness and morbidity is minimal. The fetus is the patient that might gain the most from minimal access surgery.

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L18
How to introduce new drug treatment in pregnant women

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Most drugs are not tested in pregnant women to avoid the potential harm to the mother and fetus. Additionally, if a drug is considered safe to take early in the first trimester, it may turn out to be harmful during the last few months of pregnancy as the body's physiology changes throughout pregnancy. 25% of pregnant women have been dispensed a drug for which human safety has not been established (Category C on the FDA's list). Drugs cause only 2 – 3% of all fetal congenital malformations; most deformities result from genetic, environmental, or unknown causes.

The effect of a drug on the fetus is determined by fetal age, dosage and drug potency. Drugs given before the 20th day after fertilisation may have an all-or-nothing effect, killing the embryo or not affecting it at all. Teratogenesis is not likely during this stage. The period of organogenesis (between the 3rd and 8th week) is critical for teratogenesis. Drugs reaching the embryo at this stage may have no measurable effect or may result in abortion, a sublethal gross anatomic defect (true teratogenic effect), or a permanent subtle metabolic or functional defect that may be manifested later in life (covert embryopathy). Drugs given after organogenesis (in the 2nd and 3rd trimesters) are unlikely to be teratogenic, but they may alter the growth and function of normally formed fetal organs and tissues.

How to introduce new drugs during pregnancy? In general, the pregnant women are the last to profit from new drug development. The drugs have been used for years for certain chronic disease before they (by accident) have been used during pregnancy. The main reason is the desperate need for a more potent drug than the conventional one to treat often severe illnesses during pregnancy. The risk is often minimal, if only the drug pharmacokinetic properties have been changed, e.g. by modifying the chemical structure (aminoacids) of human insulin to change the 'time action profile' to new insulin analogues. These insulin analogues, both short and long acting, are actually considered safe when used during pregnancy. A second example of potential low risk for pregnancy is the use of low-molecular-weight (LMW) heparins, which although small molecules are negatively charged impeding transplacental passage of these compounds. The LMW-heparins are nowadays considered even safer than the unfractionated heparin.

RCTs during pregnancy to prove the efficacy and especially safety of new vs conventional drugs cannot be accepted. Every drug exposure should be evaluated individually after discussions with the drug manufacturer (for toxicology, teratogenity, mutagenity) and the patient. All the safety information (pregnancy outcome, malformations, spontaneous abortions) should be collected and distributed to a common database. The manufacturers should be encouraged to take a more active role in reporting the safety data on new drugs used during pregnancy.

L19
Treatment of urea cycle defects

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The treatment goals of inherited urea cycle disorders (UCDs) are to reduce nitrogen load, prevent hyperammonaemia, prevent arginine deficiency and allow normal growth and development. A protein restricted diet alone is generally insufficient to prevent hyperammonaemia while allowing a positive nitrogen balance. Drug treatment of UCD may consist of alternate pathway activation, to eliminate nitrogen through the urine in the form of conjugated or free amino acids and/or stimulation of ureagenesis by administration of urea cycle intermediates or a cofactor.

Alternate pathway therapy includes Intravenous Ammonul® (sodium phenylacetate/sodium benzoate) used in the treatment of acute hyperammonaemia. After activation, the combination drug conjugates glycine (1nitrogen per molecule) and glutamine (2 nitrogens per molecule) that are eliminated in the urine as hippurate and phenylacetylglutamine respectively. An oral equivalent of this drug, (Ucephan®), has been discontinued and is not commercially available. Instead, a precursor of phenylacetate (phenylbutyrate, Buphenyl®) is administered orally for chronic treatment, and after conversion to phenylacetate has the same effect (elimination of glutamine). Sodium phenylacetate/sodium benzoate displays saturable, non-linear elimination, with a decrease in clearance with increased dose. Benzoate is eliminated more rapidly than phenylacetate. These "nitrogen scavengers" have allowed maintenance of nitrogen homoeostasis and growth but are not sufficient to prevent intercurrent hyperammonaemic attacks during catabolic stress. Side effects can include repugnant odour (phenylacetate), depletion of branched-chain amino acids, hypernatraemia, hypokalaemia and salicylate-like toxicity from overdosing.

Patients with proximal urea cycle disorders, including carbamyl phosphate synthetase and ornithine transcarbamylase deficiency, are supplemented with L-citrulline in addition to alternate pathway therapy, whereas those with distal disorders [(argininosuccinate synthetase deficiency (citrullinaemia type I) and argininosuccinate lyase deficiency (argininosuccinic aciduria)] are given L-arginine. In these latter disorders, arginine has a role of stimulating urinary nitrogen elimination via stochiometric excretion of citrulline or argininosuccinate. Large doses of L-arginine are particularly effective in the treatment of argininosuccinic aciduria and alleviate the need for alternate pathway drugs, while patients with citrullinaemia still need to be treated with alternate pathway drugs.

Patients with the rarest UCD, N-acetylglutamate synthase deficiency require only treatment with N-carbamylglutamate (Carbaglu®) that restores their urea production to normal and cures the hyperammonaemia. Patients with ornithine translocase deficiency (hyperornithinaemia, hyperammonaemia and homocitrullinuria syndrome), are generally treated like proximal UCD. Whether treatment of patients with citrullinaemia type II (citrin deficiency) should be similar or different than other UCD is unclear. Patients with arginase deficiency (hyperargininaemia) usually have mild hyperammonaemia and most of the pathophysiology involves arginine toxicity, thus, they are treated with an arginine restricted diet.

O1
Urinary tramadol clearance to simultaneously assess various phase I and phase II processes in early neonatal life

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Background: Iso-enzyme specific ontogeny precludes the generalisation of a simple developmental pattern for CYP activity while UDP-glucuronosyltransferase (UGT) activity also matures. Since CYP2D6, CYP3A4 and UGT are involved in tramadol metabolism, urinary clearance was used to simultaneously assess ontogeny of various phase I and II processes.

Methods: The contribution of tramadol (M), *0*-demethyl tramadol (M1, CYP2D6 mediated), *N*-demethyl tramadol (M2, CYP3A4) to overall tramadol elimination and the contribution of glucuronidated (M1G) to overall M1 (M1G/M1T) elimination were assessed in 24 h urine collections during continuous intravenous infusion[1]. Correlations with postmenstrual age (PMA) were investigated.

Results: Of the total amount of M administered, 34.5 (SD 6.1)% was retrieved in the urine of 25 young infants (PMA 25–52 weeks) and primarily consisted of M 79 (SD 18)%. M1 contributed 10 (SD 17)% and M2 contributed 3 (SD 4)%. Significant correlations between M (–0.73), M1 (0.68) or M2 (0.4) and PMA were observed. The M1G/M1T ratio was 0.30 (SD 0.14). A significant correlation between M1G/M1T and PMA (r=0.68) was observed.

Conclusions: Ontogeny of various hepatic metabolic processes in neonates was assessed by investigating urinary tramadol clearance in early neonatal life. A progressive increase in CYP2D6 and CYP3A4 activity was observed but CYP3A4 activity develops at a slower pace. Glucuronidation activity shows a fast maturation with activity at adult level from 44-46 weeks PMA onwards[1-3].

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O2
Possibility of altered pharmacokinetics of morphine in neonates treated with prolonged hypothermia

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Background: Prolonged hypothermia is a promising new approach for the reduction of hypoxic-ischaemic brain injury in neonates. Administration of analgesics is unavoidable to control shivering and stress reaction during hypothermia. There are no data about the effect of prolonged hypothermia on the pharmacokinetics in infants.

Objective: We investigated whether moderate hypothermia for 72 h results in high serum morphine levels (SM) in asphyxiated neonates, who received morphine infusion during hypothermia.

Methods: Asphyxiated term newborns were prospectively randomised for treatment with hypothermia (H) (n = 10), or for standard intensive care (SIC) (*n* = 6). Hypothermia (rectal temperature: 33–34 ^{0}C) was applied before 6 h of age, and was maintained for 72 h. All infants were treated with morphine-HCl, loading dose 50–150 microg/kg, maintenance dose 5–20 microg/kg/h. Blood samples were collected for SM determination (ELISA Opiates Reagent Pack, Abbott Diagnostics) at 6, 12, 48 and 72 h of age.

Results: In all infants SM increased with time. Infants receiving H had higher SM than infants receiving SIC at 72 h (median, [range] ng/ml: 373[149–506] vs 222[89–309] P<0.03). SM were above 300 ng/l in all but one infants receiving H, and in only one infant receiving SIC.

Conclusions: Our results show that prolonged mild systemic hypothermia in asphyxiated neonates is associated with a dramatic increase of SM. These results underline the immediate need for clinical studies to investigate the effects of hypothermia on the pharmacokinetics of commonly used drugs in infants.

O3
The effect of N-acetylcysteine on ifosfamide-induced nephrotoxicity

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Background: Ifosfamide (IF) nephrotoxicity is a serious adverse effect in paediatric patients undergoing chemotherapy despite concurrent administration of MESNA. Previous studies have shown that in addition to the renal production of chloroacetaldehyde (CAA), a toxic metabolite of IF, lower levels of glutathione (GSH) may predispose the kidney to damages by CAA. The antioxidant N-acetylcysteine (NAC) is used extensively as an antidote for paracetamol poisoning in children. Since it has been safely and effectively used clinically, the goal of this study was to test whether reversal of ifosfamide-induced nephrotoxicity can be achieved by administering NAC.

Methods: LLC-PK$_1$, a porcine renal tubular proximal cell line, was pre-treated with either 50µM BSO or 2.5 mM NAC alone followed by the addition of 1mM IF and 50µM BSO. Cellular viability was assessed by alamarBlue assay at 24 and 96 h. Intracellular and extracellular GSH and GSSG levels were determined by GSH/GSSG ratio kit and high performance liquid chromatography (HPLC), respectively. Statistical differences were assessed by one-way ANOVA.

Results: There was no significant cellular death with BSO and IF at 24 h. In contrast, there was a significant decrease in cellular viability when cells were treated daily for 96 h (P<0.05). This decrease was significantly reduced when cells were concurrently treated with NAC (P<0.05). Intracellular and extracellular GSH levels in the cells receiving concurrent treatment of NAC remained significantly lower as compared to the controls.

Conclusions: NAC protects renal tubular cells from ifosfamide nephrotoxicity. It is unlikely that NAC is protecting the cells by acting as a precursor for GSH synthesis. NAC may protect the cells by direct conjugation with CAA, acting alternatively as a nucleophile.

O4
The beneficial use of terlipressin in children with refractory vasodilatory shock after heart surgery

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Background: Terlipressin (TP), a long acting analogue of vasopressin has been used successfully in patients with refractory vasodilatory shock (RVS). However, its use in children following open heart surgery (OHS) is still limited. In this study we describe the beneficial effects of TP treatment in children with RVS after OHS.

Methods: Records of all paediatric patients after OHS with extreme RVS that were treated between January 2003 and December 2005 with TP as rescue therapy were reviewed. Data such as mean arterial blood pressure (MAP), heart

rate, urine output, lactate and oxygenation index (OI) was retrieved.

Results: Twenty nine children after OHS with the most extreme RVS who were considered near dead despite conventional vasoactive agents, were treated with TP as a rescue therapy. Eighteen patients (62%) survived. Shortly after TP administration, significant improvements in haemodynamic and respiratory indices were noted. Blood pressure increased significantly. MAP increased from 49±17 to 57±16 mmHg (P=0.002) after 10 minutes and to 64±15 mmHg (P<0.001), 24 h after beginning of treatment. Urine output increased from 1.5±0.4 to 3.0±0.6ml/kg/h 24 h after TP administration (P<0.001). Lactate levels decreased from 47.5±7.1 to 39.9±6.8 mg/dl 48 h after beginning of treatment (P=0.03). Oxygenation index decreased from 15.3±7.2 to 9.8±8.1 (P<0.001) 48 h after beginning treatment. Epinephrine dosage decreased from 0.25±0.16 to 0.09±.0.13 microg/kg/min (P<0.001) and eventually was discontinued in 13 patients.

Conclusions: Terlipressin is associated with a significant improvement in haemodynamic, respiratory and renal indices in children with extreme RVS after OHS. Further studies are needed to prove TP's safety and efficacy in children with RVS

O5
Fatal opioid toxicity in a breastfed infant of a codeine using mother

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We describe the first fatality of a baby through morphine ingested in breast milk. A healthy mother received high dose codeine due to epiphysiotomy pain. At 7 days of life the infant began to be somnolent and not to feed well. The baby died at home at 14 days. Postmortem morphine levels were highly toxic (90 ng/ml), tenfold above those seen in infants receiving morphine. Milk levels were 80 ng/ml, tenfold above those measured in milk after typical maternal codeine dosing. Genotyping revealed that the mother was an ultra rapid metaboliser of 2D6, the CYP450 enzyme catalysing the O demethylation of codeine to morphine. The rate of this polymorphism is 1% among Caucasian, but up to 30% in some ethnic groups (e.g. Ethiopians).

In North America thousands of women receive codeine postpartum for pain associated with Caesarean section or epiphysiotomy. This risk must be communicated to doctors and mothers. Potential approaches include: not using codeine, following the baby and mother for signs of opioid toxicity, in suspected cases of toxicity to give naloxone, and genotyping of mothers receiving codeine.

O6
GABA excitation and neonatal midazolam

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Many infants are exposed to considerable pain as a result of disease processes, surgery or intensive care procedures. Management of these patients is complicated by a lack of understanding of the fundamental mechanisms underlying sensory processing in infants[1]. 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[2].

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)[3]. Previous work in our laboratory 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.

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.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.

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O7
Pharmacoepidemiology of Attention Deficit and Hyperactivity Disorder (ADHD) in school aged-children: the Italian national register

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Background: Mental health disorders (MHD) in children and adolescents will increase by 50% in 2020 and will become the fifth most common cause of morbidity. MHD prognosis is directly linked to their early management. Improving detection and prevention of MHD is therefore a real need. MDH are defined on the basis of recognised criteria established on international consensus of specialists. Today it appears necessary to involve all education and health care professionals in the promotion of mental health in children and to educate them to recognise the early signs of emotional and behavioural problems.

Methods: Prescription of ADHD pharmacological treatment will only be possible in Italy under strict control based on diagnosis and staging performed at reference centres accredited by the Italian National Institute of Health. Suspected ADHD children should be referred by paediatricians, schools, or parents' associations to these centres for diagnosis confirmation and included in a national register for a prospective observational period of 24 months. The objectives are to insure the standardisation of ADHD management and the assessment of long-term safety.

Results: The warning signs of ADHD within a specialist environment should result in a rapid diagnosis that makes early intervention possible. The registry will ensure the shared care with specialists and give precise indicator of prevalence and incidence of ADHD.

Conclusion: The Italian national register on ADHD will contribute to optimise early management of ADHD and may be extended to manage all other MHD in children.

O8
Alcohol and illicit drug use amongst adolescents presenting to the emergency department

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The highest risk of illicit drug use is between the ages of 12 and 25 years. All epidemiological studies of adolescent alcohol and illicit drug use in Israel to date have been conducted in schools, households and shelters for high risk teenagers.

Objective: To characterise the teenagers that present to the Emergency Department (ED) of a general hospital with regard to the presenting complaints, demographic and socioeconomic characteristics, and the use of particular drugs.

Methods: The study was conducted in two stages: (1) Retrospective, where the charts of children under 18 who had presented to the ED at "Assaf Harofeh" Medical Center between 01/01/95 and 31/01/2002 were reviewed and (2) Prospective phase, collecting information about all adolescents who presented to the ED between 01/02/2002-30/06/2003.

Results: 30 charts were identified retrospectively and 42 in the prospective phase. The average age was 16.7 years. 17 patients (24%) were of Russian extraction, 21% Arab, 10% Ethiopian and 41% were of other Jewish origin. 27 patients (37.5%) were in secular educational institutions, 6 in religious educational institutions and five in residential institutions. 17 were not currently studying at all.

50% used drugs, 43% drank alcohol and 10% did both. The most frequently used drug was marijuana – 12 (28%), 10 (23%) used hashish, 7 (16%) used opiates, 7 (16%) used ecstasy, 4 (9%) used hallucinogens and 4 (9%) used amphetamines. Six patients used more than one drug.

The most common presenting complaint was related to the effect of the drug on the central nervous system (41%), followed by gastrointestinal complaints (12), suicide attempts (9) and two with fainting episodes. On presentation, 52 (72%) patients were fully conscious, 16 were semi-conscious and two were unconscious.

Conclusions: Prospectively, 42 patients presented in 17 months as compared to 30 patients in the retrospective part (5 years). This difference is most likely due to the awareness of the ED staff of the search for alcohol and illicit drug use. It is possible that alcohol and illicit drug use is in fact rising in Israel. Most of the adolescents were from lower socioeconomic levels, new immigrants, or from poor Arab neighbourhoods. However, members of well-established families were also represented. Alcohol and illicit drug use is not unique to secular society but has in fact reached religious high schools as well. There is a need to invest efforts among the hospital staff and in particular those working at the ED in order to increase their awareness to the problem.

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O9
Safety in paediatric clinical trials – 7 year review

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Background: The need for clinical trials of medicines in children is now well established. We wished to evaluate the extent of drug toxicity in association with these clinical trials.

Methods: A literature search was conducted on Medline to identify clinical trials involving oral and intravenous medication used in children from 1996 to 2002. The areas of oncology and HIV were excluded. The original papers were reviewed to determine safety monitoring and the number of children who experienced an adverse drug reaction (ADR).

Results: 745 trials were identified over the seven year period. Possible ADRs were reported in 453 (61%) studies. The suspected ADRs were mild in 270 trials and moderate in 84 trials. Of the 84 trials with moderate adverse events, 41 had a significant increase in ADRs in the treatment group. 99 trials reported at least one possible severe ADR (13%), and of these, 27 reported a significant increase in the treatment group. Only 16 trials (2%) mentioned an independent safety monitoring committee. Five trials were terminated early for safety reasons, all had a safety monitoring committee. Deaths occurred in 74 (10%) of studies, most due to the severity of the underlying condition. In three studies deaths were more frequent in the treatment group.

Conclusions: Conducting clinical trials in children is important. ADRs are a significant problem and therefore good trial design is needed to detect trends in adverse events. More paediatric trials need a safety monitoring committee.

O10
The Paediatric Unit at the Coordination Centre for Clinical Trials, Heidelberg: an approach to improve quality and conduct of clinical drug trials in children

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Although children and adolescents represent about 25% of the European population, 40% to 70% of the children receive drugs prescribed in an unlicensed or off label manner. The EU regulation "Better Medicines for Children", expected to come into force in 2007, aims at improving the drug therapy of children. The EU regulation will require the member states of the EU to establish paediatric network structures.

Funded by the German Ministry of Education and Research in 2003, the Paediatric Unit was established as a part of the Coordination Centre for Clinical Trials. It aims at building up competence, skills and infrastructure for clinical drug trials in children, offers support and coordination for multicentre clinical drug trials in children. Furthermore, it is developing means and methods to ensure high quality and professional conduct of studies.

To establish a paediatric network in order to optimise conduct of studies, it is part of the PAED-Net, a competence network with infrastructure for planning and performing paediatric multicentre studies in paediatric units of Coordination Centres for Clinical Trials at 6 locations in Germany: Freiburg, Heidelberg, Cologne, Leipzig, Mainz, and Muenster, as well as a central coordinating unit located in Mainz. The PAED-Net is funded by the German Ministry of Education and Research.

The Paediatric Unit and the German PAED-Net contribute to a competent high-quality conduct of clinical drug trials in children in order to optimise paediatric drug therapy and may serve as a model for the paediatric networks required by the upcoming EU regulation.

O11
The French Network of Paediatric Clinical Investigation Centres

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Background: The network aims at stimulating clinical research, both investigator-initiated and industrially sponsored, in the area of drug evaluation in children and at participating in training and education. The Network of Paediatric Clinical Investigation Centres (CIC) is a national network set up in 2001, consisting of seven centres. The Paediatric CIC is integrated into teaching hospitals and collaborate with medical and technical departments, INSERM and university research units. It contributes to technical innovations, has facilities designed for the conduct of research in children and provides support to investigators, from design through the conduct of clinical research protocols. The CIC network also supports parents and their children during participation in medical research.

Results: 136 protocols were ongoing in 2006: 60% in the area of drug evaluation and 40% in physiology and pathophysiology. 28% were single centre, 41% were multicentre at the national level and 29% multicentre with international sites. Most paediatric subspecialties were involved, including neonatology, endocrinology, hepatology-oncology and paediatric surgery. In addition, translational research in endocrinology (therapeutic effect of leptin in lipo-atrophic diabetes) and neurosciences (pathophysiology, prevention and treatment of neonatal ischaemic brain lesions) were initiated. The network now aims at organising connections with European and American networks in order to optimise clinical research in children.

O12
Discovery of a novel transcriptional control of human CYP3A constitutive expression

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Background: In contrast to induction mechanisms, the control of CYP3A constitutive expression, including fetal CYP3A7 expression, is unknown. In this study, we describe a novel observation that CYP3A constitutive expression is dependent on ambient osmotic environments. We further test a hypothesis that the tonicity responsive enhancer binding protein (TonEBP) mediates the phenomenon.

Methods: Human intestinal C2bbe1 cells, a subclone of Caco2 cells, were exposed to various external tonicity. Real-time RT-PCR and western blotting were used to analyse gene and protein expression. TonEBP expression plasmid, siRNA, and dominant-negative TonEBP were used for gain- and loss-of-function assays. Luciferase-based reporter, electrophoretic mobility shift (EMSA), and chromatin immunoprecipitation (ChIP) assays were used to identify the TonE element within the CYP3A gene cluster.

Results: There was significant tonicity-dependent increase in CYP 3A4, 3A7 and 3A5 mRNA (5-10-fold increase at 400 mOsm/kg) and protein expressions with no appreciable change in PXR. This was confirmed in the primary culture of human colon, and the other cell lines of human intestinal and hepatic origins. Reporter assays and EMSA revealed an active tonicity responsive-enhancer (TonE) sequence within a *CYP3A7* intron. ChIP assay confirmed TonEBP binding to the intronic enhancer in a native DNA context.

Conclusion: Human *CYP3A* constitutive expression is under the influence of ambient osmolality via TonEBP-TonE signaling. In particular, fetal *CYP3A7* constitutive expression is driven by ambient tonicity through the intronic enhancer responsive to external tonicity. The *CYP3A7* intronic enhancer may also serve as a long-range enhancer for *CYP3A4* and *CYP3A5*.

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M1
Views of paediatricians and researchers on the ethics of paediatric research and using healthy children as volunteers

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Background: Ethical problems are often quoted as a reason not to perform trials in children. Little is known about current researcher's views.

Methods: A questionnaire based study in the UK and Canada, including short scenarios. First scenario - new antibiotic for Cystic Fibrosis (CF) to be tested in healthy children, a pharmacokinetic study. Second scenario - a double blind placebo controlled trial for a new analgesic following tonsillectomy.

Results: 97 questionnaires completed (48 UK and 49 Canada). First scenario - 23% in the UK and 45% in Canada felt happy entering children. 8% and 34% felt ethical approval would be granted. Concerns were: use of healthy children (83% and 59%), venepuncture (31% and 8%) and drug safety (21% vs 24%). Many (56% and 43%) felt the trial should be carried out in the CF population. Second scenario - 23% in UK and 41% in Canada felt happy entering children. 25% vs 41% felt the trial would receive ethical approval. Main concern was the use of placebo (75% and 66%) and an acute comparison trial with another analgesic would be preferable (69% and 59%). Just under half, in both countries, felt a child should only participate if they receive direct benefit. 83% and 69% felt children could be harmed by participation in trials.

Conclusion: Using healthy children and placebo in clinical trials causes concern, with similar attitudes in the UK and Canada. Study protocols need to take this into account if they are going to receive the backing of investigators and ethical approval.

M2
Survey of administration of oral medicines to children and the problems encountered

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Background: Many children require liquid medicines, however many drugs are not available in a licensed liquid formulation. Nurses therefore need to manipulate solid dose forms to produce a preparation that the child can take. Few studies have examined this. This study aimed to quantify and describe the number of episodes, time taken and medicines involved when nurses need to manipulate medicines (e.g. crushing tablets, opening capsules) in order to administer them to a child.

Method: Drug administrations were observed on paediatric wards in Queen's Medical Centre, Nottingham and the Derbyshire Children's Hospital. The time taken and any manipulations made to the drugs before administration were recorded.

Results: 198 drug administrations to 100 children were observed. 9.6% of drugs administered required a manipulation and 10% children received a manipulated drug. The administration of a manipulated drug took significantly longer, on average twice as long. The most frequent manipulation was for tablets to be crushed and dissolved in water prior to administration. Manipulations of medicines were required across all age groups. Liquid medicines were required by two-thirds of children and took significantly longer to administer than tablet forms. Children with a feeding tube required manipulated medicines four times more often than those without.

Conclusion: The need to manipulate drugs in order to be able to administer them to children is common on paediatric wards. It increases the time taken to administer drugs with a significant impact on nursing staff resources.

M3
The impact of educational intervention programmes on pain management in a paediatric emergency department

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Background: Management of pain and anxiety is an important part of patient care in the paediatric Emergency Department (ED). Even though it has improved significantly over the past few years, it is still suboptimal. The objective of this study was to evaluate the effect of informal and formal education on pain and anxiety management in the paediatric ED.

Methods: Management of pain and anxiety was assessed by comparing the use of analgesics and sedatives during 3 phases: A) year 2000 (baseline), B) years 2001–2002 (informal teaching) and C) year 2004 (following a structured simulation-based training in paediatric sedation and analgesia).

Results: During period B there was a significant increase in the yearly use of eutectic mixture of local anaesthetics (EMLA) (RR=2.63, CI:1.23–5.6), ibuprofen (RR= 14.16, CI: 8.73–22.98), midazolam (RR= 1.68, CI:1.39–2.03) and nitrous oxide (N_2O) in comparison with period A, with an additional increment of the first three medicines during period C. There was no change in the use of ketamine,

morphine and pethidine during period B. Whereas, during period C, a significant increase in the use of ketamine and morphine was demonstrated (RR=24.56, CI:10.71–56.3 and RR=3.07, CI:2.12–4.44 respectively), while the use of pethidine (RR=0.68, CI:0.49–0.94) and N_2O (RR= 0.46, 95% CI: 0.32–0.67) declined significantly.

Conclusions: Educational interventions have a clear impact on pain and anxiety management demonstrated by the subsequent change in the use of sedatives and analgesics and should be provided to paediatric ED physicians. Informal teaching affected mainly the use of milder sedatives and analgesics, while formal structured training influenced the use of opioids and dissociative agents.

M4
Analysis of individual case safety reports related to drug therapy in children in the Swedish adverse drug reaction database

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Background: Drug therapy is often introduced in children when use has been established in adults. At this point knowledge of specific risks in children is limited. Risk management of drugs for children is therefore dependent on observations from clinical use. The aim of the present study was to investigate the type and frequency of individual case safety reports (ICSR) per million prescribed defined daily doses (DDD).

Methods: The Swedish database for adverse drug reactions (SWEDIS) was analysed for ICSR in children 0–14 yr old in 2003–2005. Corresponding prescription sales data was obtained from the database Xplain. Frequency of ICSR per million DDD was calculated.

Results: ICSR concerning children constituted 16-23% of all ICSR reported to SWEDIS 2003-2005. Five subgroups of drugs in which the number of reports was highest were identified; vaccines, antibiotics, antidepressants, psychostimulants, respiratory drugs and antihistamines (Table 1). The frequency of ICRS per million DDD in antidepressants is overestimated since antidepressants use in expectant mothers, whose children may experience an ICRS, is not included in the figure for DDD supplied. Serious ICSR, mainly referred to need for hospitalisation, was observed in all five groups, being most frequently reported for antibiotics.

Conclusion: Reports regarding adverse drug reactions in children is limited. There is a need for a more frequent reporting to better understand and evaluate the balance of risk-benefit of drug use in children.

M5
Rizatriptan is consistently effective in migraine attacks in children

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Background: Migraine is a common disease among children. Although all attacks are not adequately controlled with simple analgesics, none of the orally administered triptans is available for children. Study objective was to examine the efficacy of rizatriptan and the consistency of response in migraine attacks of children and adolescents.

Methods: A double-blind, placebo controlled three-way crossover trial in 6 to 17 y old migraine patients, conducted in two paediatric outpatient clinics. Two doses of rizatriptan and a matching placebo were administered at home during three attacks. Rizatriptan dose was 5 mg (body weight 20 to 39 kg), or 10 mg (40 kg or more). The primary efficacy endpoint was headache relief by two grades on a 5-grade face scale at 2 h.

Results: Ninety-six patients used all three treatments, ten used two and ten only the first. At 2 h, the primary endpoint was reached twice as often after both treatments of rizatriptan (1st: 74%, *n*=71/96; 2nd 73%, *n*=70/96) as after placebo (36%, *n*=35/96) (*P*<0.001). Already at 1 h, rizatriptan was clearly superior, as headache relief was reported by 50% (*n*=48/96) and 55% (*n*=53/96) of children after the first and the second dose of rizatriptan, compared to only 29% (*n*=28/96) after placebo (*P*=0.004). All the other endpoints also favoured rizatriptan. Efficacy of rizatriptan was very constant over the two treated attacks in both 5 and 10 mg treatment groups. No serious adverse effects were observed.

Conclusion: Rizatriptan is an effective and well-tolerated treatment for migraine attacks in children over 6 yr of age.

M6
Cyclooxygenases and prostaglandin receptor expression in articular cartilage of the rat – an in situ study

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Background: Cyclooxygenases are involved in various physiological and pathophysiological conditions. Cyclooxygenase-1 plays a role as a housekeeping enzyme and is detectable in nearly all tissues, whereas cyclooxygenase-2 is inducible for example in inflammation but also in ontogenic processes. The effects of prostaglandins are mediated by four isoforms of prostaglandin receptors (EP-1 – EP-4). The role of cyclooxygenases in bone development and metabolism is already known from various *in vitro* systems. Our group has already demonstrated the role of cyclooxygenases in the growth plate *in situ*. However, the expression and distribution of cyclooxygenases in articular cartilage is not yet known. In the present study we examined the expression and spatial distribution of COX-1, COX-2 and EP1 – EP-4 in the articular cartilage of the tibia in young Sprague Dawley rats.

Methods: Frozen sections (4 µm) from 4 week old (60–80g) Sprague Dawley rats were analysed by the APAAP-method with polyclonal rabbit antibodies directed against COX-1, COX-2 and prostaglandin receptors (EP-1 – EP-4).

Results: Articular cartilage of young Sprague Dawley rats showed expression of both isoforms of cycloocygenases and EP-1 – EP-4 receptors with a characteristic distribution: the apical cell layers are negative for these antigens.

Conclusion: Further studies by molecular techniques are needed including microdissection to verify the special distribution of cyclooxygenases and prostaglandin receptors. Based on this finding, analysis of human analysis of human

Table 1 Individual case safety reports for children 1–4 yr old and 5–4 yr old, respectively, in 2003–2005 in SWEDIS. Corresponding prescription DDD and frequency ICSR per prescribed DDD is also presented. For vaccines, no data on sales for the age groups was available

Drug class	1 – 4 yr old				5 – 14 yr old			
	ICSR total	ICSR serious	DDD supplied	Frequency ICSR per million DDD	ICSR total	ICSR serious	DDD supplied	Frequency ICSR per million DDD
Antibiotics	22	8	3 978 293	5.5	20	9	7 258 076	2.8
Vaccines	966	116	-	-	849	26	-	-
Antidepressants	19	17	4 394	4 324	4	0	1 526 359	2.6
Psychostimulants	0	0	3 878	0	20	2	3 857 040	5.2
Respiratory drugs	31	3	10 208 790	3.0	27	1	22 682 373	1.2
Antihistamines	6	0	1 275 525	4.7	10	1	14 989 566	0.7

embryonic tissue and tissue from children are ongoing to analyse the role of cyclooxygenases and prostaglandin receptors in the development and metabolism of articular cartilage.

M7
Population pharmacodynamic modelling of propofol and midazolam in non-ventilated infants after major craniofacial surgery

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Background: Although propofol and midazolam are widely used for sedation in the adult intensive care, information on pharmacodynamics in non-ventilated infants after major surgery is scant. In this study, population pharmacodynamic models for propofol and midazolam are described using the validated COMFORT-Behaviour (COMFORT-B) scale and the Bispectral Index (BIS).

Methods: Of 55 infants (aged 3–24 months) admitted to the Paediatric Surgery Intensive Care following major craniofacial surgery, nine infants did not need sedative medication, 22 received propofol and 24 midazolam, based on the COMFORT-B score. BIS values were recorded simultaneously. Population pharmacodynamic modelling was performed using NONMEM V.

Results: In infants who received no sedative, depth of sedation was a function of baseline at arrival, post-anaesthesia effect (E_{max} model) and circadian night rhythm (cos model). In agitated infants, depth of sedation was best described by baseline, post-anaesthesia effect and propofol or midazolam effect (E_{max} model). The EC_{50} for propofol was 1.76 mg/l (CV of 47%) on the COMFORT-B and 3.71 mg/l (CV of 145%) on the BIS, the latter being comparable to adult values (3.91 mg/l). For midazolam, the EC_{50} was 0.58 µmol/l (CV of 89%) on the COMFORT-B. Using the BIS, in 57% of the infants, the effect of midazolam could not be characterised.

Conclusion: The effect of midazolam in infants is less predictable than propofol, which implies that propofol should be further studied in the paediatric intensive care, taking into account safety recommendations. For both sedatives, individual titration remains important.

M8
New scaling factor for dosing in (preterm) newborns and infants based on morphine and its glucuronides as a model drug

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Background: In order to predict drug concentrations in preterm newborns from 500 g to infants of 3 yr old (18 kg), we studied the influence of different patient characteristics (body weight, birth weight, postnatal age, postconceptional age, gestation) on the pharmacokinetics of morphine and its glucuronides (morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G)) as continuous covariates.

Methods: The analysis was based on 2159 morphine and glucuronide concentrations from 248 infants ranging in body weight from 500 g to 18 kg (median 2.8 kg), receiving 2400 µg/kg/24h intravenous morphine[1,2]. Population pharmacokinetic modelling was performed using NONMEM V.

Results: Body weight proved to be the most predictive covariate for both formation clearances to M3G and M6G and elimination clearances of these glucuronides. The clearances could all be described using an allometric equation based on body weight, with an exponential scaling factor of approximately 1.5. For the volumes of distribution, this factor was not significantly different from 1. Postnatal age less than 10 days was an additional covariate for formation clearance to glucuronides, resulting in 25% higher concentrations of morphine.

Conclusion: In contrast to the previously reported value of 0.75, the exponential scaling factor for formation and elimination clearance proves to be 1.5. This suggests that drugs undergoing glucuronidation should be given in a fixed dose expressed in µg/kg$^{1.5}$ instead of µg/kg in order to obtain similar concentrations in all infants ranging from 500 g to 18 kg body weight. For term and preterm newborns younger than 10 days, formation clearance to glucuronides is impaired.

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M9
Octreotid treatment in congenital chylothorax with Opitz G/BBB syndrome

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Congenital chylothorax may occur in certain genetic syndromes. Here we present a clinical case of Opitz G/BBB syndrome (OS) complicated by congenital chylothorax. Our patient (3.2 kg male of a 27-year-old primigravid mother) was delivered at 37 weeks of gestation by Ceasarean section. The delivery was induced for a prenatally diagnosed pleural fluid. The patient was intubated and ventilated immediately after delivery. A chest radiograph revealed a right-sided pleural effusion. During thoracocentesis, 150 ml of straw-coloured fluid with triglyceride content of 7.8 mmol/l was obtained. The boy also had bilateral cleft lip and palate, hypertelorism, hypospadias, right cryptorchidism, a left hydrocele, widow's peak, prominent forehead, low-set, posteriorly angulated ears and flat, broad nasal bridge. The patient was treated by repeated thoracocenteses, total parenteral nutrition and administration of octreotide (40 µg/kg/day). He remained stable and was extubated on day 8, with removal of the chest drain on day 13 of life. He was bottle-feeding and discharged from the NICU. However, on day 25, severe aspiration necessitated re-intubation and mechanical ventilation and he died on day 30. Karyotype was normal, as were results of *MID1* mutation analysis and 22q11.2 and 13q subtelomeric FISH. The phenotypic findings of our patient were consistent with OS but we could not support our diagnosis genetically. This may be due to the fact that the genetic cause in a large number of OS patients still remains unknown. This is the first report of OS complicated by congenital chylothorax. The chylothorax of our patient was successfully treated with octreotide.

M10
Child neurodevelopment following exposure to venlafaxine in utero, unexposed siblings as comparison groups: preliminary results

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Background: Venlafaxine (VLF) is an antidepressant drug often used by pregnant women. Its possible adverse effects on fetal CNS development have not been studied. The present study will fill the knowledge gap.

Objectives: To assess long-term neurodevelopment of children exposed to VLF during gestation.

Methods: Prospective cohort - controlled, matched, and blinded. Assessment of five groups of mother-child pairs: exposed to VLF (*n*=32), exposed to other SRIs (n=29), healthy controls (*n*=42), and two groups of siblings (*n*=15). Siblings were unexposed relatives of children from the VLF or 'other SRIs' groups. Primary outcome: WPPSI-III Scales of Intelligence. VLF exposed children will be compared with those of children in control groups and their non-exposed siblings.

Results: There were no differences between the VLF and healthy control group in maternal IQ or mother-child physical characteristics. In terms of Full Scale IQ, Performance IQ and Verbal IQ there was no difference between the SRIs and VLF groups (103±10 vs 105±12; 102±11 vs 102±15; 103±11 vs 105±12), the SRIs group and their siblings (103±10 vs 104±8; 102±10 vs 104±8; 103±11 vs 106±12), or the VLF group and their siblings (105±12 vs 100±8; 102±15 vs 105±7; 105±12 vs 95±10). Healthy controls scored significantly higher than the VLF group and the other 3 groups in Full Scale IQ, Performance IQ and Verbal IQ (P= 0.011; 0.041; and 0.028 respectively).

Discussion: Preliminary results show that factors such as maternal depression, genetics, and environment (not the antidepressant medications) are strongly associated with the child's cognitive abilities. Assessment of siblings helps to verify the impact of these factors and is possibly the strongest evidence in drug safety studies.

M11
Drug related problems and *off-label* drug treatment in children at a regional drug information centre

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Background: There is a lack of documentation concerning paediatric efficacy and safety for many drugs, which can contribute to *off-label* drug treatment and increase the risk for adverse drug reactions in children. Our aim was to analyse the characteristics of *Questions and Answers* (Q&A) at a drug information centre (DIC) regarding *drug related problems* and *off-label drug treatment* in children.

Methods: All Q&A concerning children 15 years or younger at a DIC in Stockholm, Sweden during the years 1995-2004 were analysed with respect to the main drug related problem, drug/s and drug group/s, paediatric labelling of the drug/s and age and sex of the patient. Q & A involving *off-label drug treatment* were divided into those where additional literature information was found and those where no additional information was found.

Results: We identified 249 Q&A concerning paediatric drug treatment. Each question addressed on average 1.5 drugs. More than two-thirds of the Q&A concerned adverse drug reactions and paediatric drug choice or dosing. Every second Q&A was classified as *off-label*, with psychotropic drugs being the most common. In half of all *off-label* Q&A, documentation concerning paediatric drug efficacy and safety outside the Swedish catalogue of medical products was found. Most Q&A concerned newborns and infants. However, the *off-label* proportion among questions was highest in adolescence.

Conclusions: Off-label drug treatment is a common phenomenon among paediatric Q&A at a DIC. The DIC can often provide additional, literature based information, hopefully improving the safety of drug use in children. There is still, however, a big need for clinical documentation of drug use in children.

M12
Antenatal betamethasone and renal drug clearance in preterm neonates

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Introduction: There is conflicting evidence on the potential impact of prenatal betamethasone on renal clearance[1,2]. We therefore evaluated the effect prenatal betamethasone administration had on vancomycin pharmacokinetics in the first month of postnatal life in preterm infants with a gestational age of 24 to 34 weeks.

Methods: Population pharmacokinetics of vancomycin in neonatal life (< 29 days) were estimated (NONMEM) during 262 events in 214 preterm neonates (602 concentration profiles, gestational age 30.4, range 24–34 weeks; postnatal age 11.9, range 1–27 days; weight 1.30, range 0.42–2.6 kg). Covariate analysis included weight, postmenstrual age (PMA), serum creatinine, Apgar score, administration of inotropics, blood culture proven infection, use of respiratory support, administration of ibuprofen as well as maternal indomethacin or betamethasone administration.

Results: A one-compartment linear disposition model with zero order input (1 h IV infusion) and first order elimination was used. Clearance (CL) increased from 0.78 L/h/70kg at 24 to 2.01 l/h/70kg by 34 weeks PMA. Between subject variability (BSV) for CL was 18.6%, between occasion variability was 12.2%. Ibuprofen administration reduced clearance, but this effect was attributable to reduced creatinine clearance. The use of positive pressure ventilation also reduced clearance by 5%. Prenatal betamethasone had no impact on subsequent vancomycin clearance. Overall, 82% of the variability of CL was predictable. Weight explained 49%, PMA 18% and renal function 34.1%.

Conclusions: Prenatal betamethasone had no impact on vancomycin clearance. Size, renal function and postmenstrual age contributed to clearance variability in preterm neonates.

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M13
Circulatory effects of antenatal betamethasone therapy in low birth weight infants

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Background: There is still need to further document the impact of prenatal steroids on various extrapulmonary outcome variables like cardiovascular stability[1,2]. We would therefore like to report on the prescription of dopamine in the first week of life in a cohort of 282 LBW infants (i.e. < 1500g) of whom 243 (86%) survived until discharge.

Results: The table shows data as median (range)

	Betamethasone	No betamethasone
Number	178	59
GA (w)	29 (24–34)	30 (24–35)
Birth weight (g)	1142 (SD 272)	1062 (SD 303)
CRIB score	2 (0–13)	2 (0–13)
Inotropics < day 7	38%	46%
Duration of inotropics (h)[a]	0 (0–168)	0 (0–144)
Duration of inotropics (h)[b]	50 (4–168)	56 (8–144)

[a]All survivors. [b]Only LBW infants treated with inotropics.

Conclusions: We were not able to document any difference in the administration of inotropics in the first week of life in LBW infants. There is still uncertainty on the impact of prenatal steroids on various extra-pulmonary outcome variables. Since the positive effect of maternal administration of steroids on neonatal RDS was repeatedly demonstrated, a RCT approach to assess the impact of prenatal steroids on these extra-pulmonary outcome variables is no longer ethical or feasible. However, prospective collection is still of clinical relevance especially if we take into account that the large RCT studies were performed in the 1980s and 1990s and therefore, potentially only in part reflect the populations admitted in our units[3].

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M14
Use of antiemetic drugs during pregnancy in Sweden

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Background: More than one-half of all pregnant women suffer from nausea and vomiting during pregnancy (NVP), primarily during the first trimester.

Methods: Prospectively ascertained information on drug use during pregnancy was obtained from the Swedish Medical Birth Register during the period July 1, 1995 to 2002. Antiemetics (antiemetic antihistamines, dopamine modulators, and ondansetron) primarily used for NVP were studied, and women reporting the use of these drugs were compared with all women who gave birth during the study period.

Results: Use of these antiemetics was reported in 4.5% of the pregnant women - 86% of whom reported their use before the first antenatal visit (usually weeks 10–12). Meclozine, followed by other antihistamines, accounted for 68% of the drugs reported. Young maternal age, multiparity, non-smoking, and a period of unwanted childlessness increased the probability of using any of the antiemetics during pregnancy. Women with low education used these drugs more often than women with a relatively higher education. Neonates born to women who used any of the antiemetics had a reduced risk for low birth weight, prematurity, being small-for-gestational age, and having a malformation. No specific differences were observed with respect to the outcome following a comparison of different antiemetic drugs.

Conclusions: Women using antiemetics as a rule have a better delivery outcome than other women, probably due to an effect of a well-functioning placenta, which is associated with NVP. There were no signs of any significant teratogenicity of the drugs studied, but for some drugs the number of exposures was low.

M15
P-glycoprotein in human placentas: use of a laser micro dissection to isolated trophoblastic to fetal endothelial cells

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Background: P-glycoprotein (P-gp) is an ATP-dependent drug efflux transporter implicated in the transfer of compounds from maternal to fetal side. Several authors found that P-gp was expressed on the border of the syncytiotrophoblast plasma membrane; we found a different location in the fetal endothelial cells with C494 monoclonal antibody.

Methods: In a multicentre prospective controlled study after informed written consent, aliquots of chorionic villi were immediately frozen in liquid nitrogen after delivery. Samples were stored at – 80°C. RNA extraction was performed after both macro and micro dissection. Laser micro dissection was used to collect up to 5000 cells either of trophoblastic or fetal endothelial cells. Transcripts from MDR1 gene as well as from the housekeeping genes 18 S, beta-actin and GAPDH were quantified by real time PCR (TaqMan).

Results: 62 full-term and preterm human placentas were collected. 39 were treated with betamethasone. Five full-term human placentas were micro dissected from uncomplicated deliveries. P-gp mRNA was found both in trophoblastic [89,958 copies /ng tRNA] and fetal endothelial cells [12,487 copies /ng tRNA]. P-gp mRNA was found both in maternal surface [73,492 copies /ng tRNA] and chorionic plate [38,015 copies /ng tRNA].

Conclusion: Our findings suggest that P-gp mRNA expression is higher in the trophoblastic cells in maternal surface than in the fetal endothelial cells. It would contribute to limitate the maternofetal transport of xenobiotics across the placental barrier.

M16
Polymorphism of thymidylate synthase and tolerance to the maintenance chemotherapy for children with acute lymphoblastic leukaemia or lymphoma

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Background: Methotrexate (MTX), the key drug for acute lymphoblastic leukaemia (ALL) and lymphoblastic lymphoma (LBL), exhibits its anti-cancer effect by inhibiting thymidylate synthase (TYMS), an essential enzyme for proliferating cells. *TYMS* is highly polymorphic at tandem-repeat sequence in its promoter region containing either two (2R) or three (3R) 28-bp repeat. The 3R/3R yields higher expression of TYMS with greater enzyme activity. It follows that children with ALL with 3R/3R have a shorter event-free survival.

Objective: To evaluate the association between polymorphism of *TYMS* and tolerance to the maintenance chemotherapy with MTX in children with ALL or LBL.

Methods: Polymorphism of *TYMS* and clinical data concerning tolerance to the maintenance chemotherapy in 20 children with ALL or LBL were analysed retrospectively. The oral dose of MTX was first set at 25 mg/m^2 once a week and mercaptopurine at 40 mg/m^2 a day. Those doses were adjusted in the course of the treatment according to the white blood cell count.

Results: Thirteen patients had 3R/3R and 7 patients had 2R/3R. Patients with 2R/3R, as compared to those with 3R/3R, had higher likelihood of discontinuation of the maintenance chemotherapy due to treatment related toxicities (odds ratio 3.2, 95% CI: 1.3–7.6, P=0.01). There was no significant association between *TYMS* polymorphism and the average dose of MTX and mercaptopurine administered during the maintenance chemotherapy.

Conclusion: TYMS polymorphism might be related to tolerance to the maintenance chemotherapy consisting of MTX and mercaptopurine for children with ALL or LBL.

M17
Monitoring of cyclosporine in paediatric renal transplant recipients

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Background: Although cyclosporine has been widely used in paediatric renal transplantation, little is known on its pharmacokinetics in children. The aim of the study was to evaluate the influence of cyclosporine exposure on kidney graft rejection.

Methods: 97 children, transplanted between 1997 and 2004, were included. Children received cyclosporine alone or associated with either azathioprine or mycophenolate mofetil. 209 AUC (0–12 h), drawn prior to the first rejection, were estimated by the trapezoidal rule. Threshold AUC (0–12 h), defined as mean AUC (0–12 h) minus standard deviation of AUC (0–12 h), were calculated for each associated immunosuppressant, and each post-graft period. The relation between the rate of AUC (0–12 h) over the threshold and the rejection risk was tested.

Results: No statistically significant difference between treatment groups was found for the three latter post-graft

periods (P>0.05), so a single threshold was calculated for each. AUC (0–12 h) thresholds (μg.h/L) by stratum are presented in the following table:

AUC (0–12 h) values

Associated drug	Post-graft period (months)			
	<1	1–3	3–12	>12
Azathioprine	5583	3549	3135	2072
Mycophenolate	3678			
None	4185			

Patients in whom the rate of AUC (0–12 h) over the threshold was at least 50% were separated from those in whom that rate was below 50%. There were four times more rejects in children in whom less than 50% AUC (0–12 h) were superior to the threshold (OR=4; IC95%=1.28–12.5).

Conclusion: There is an incidence of cyclosporine under-exposure on the rejection risk, whatever associated treatment and post-graft period. Those results allowed us to define target cyclosporin AUC (0–12 h), implemented in routine for the monitoring of renal transplant children.

M18
Impact of inflammation on duodenal mRNA expression of CYP3A and P-gp in patients with Crohn's disease

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Background: Cytochrome P450 3A subfamily (CYP3A) and P-glycoprotein (P-gp) are both expressed in the enterocytes, reducing the bioavailability of orally administered drugs that are substrates of the CYP3A/Pgp system. *In vitro*, pro-inflammatory agents decrease CYP3A levels but their effects on P-gp expression remain controversial. Crohn's disease (CD) is a chronic inflammatory bowel disease and preliminary data in humans have showed that both CYP3A and P-gp mRNA, protein content and activity levels were higher in various tissues in CD patients compared with non affected individuals. The aim of our study was to analyse the impact of systemic inflammation on the expression of CYP3A and P-gp in human normal duodenal tissue.

Methods: We compared CYP3A and P-gp mRNA expression in 19 non-inflamed duodenal biopsies from children with CD before any treatment with 19 normal biopsies. We used a real time RT-PCR technique and villin for normalisation.

Results: The expression of the three CYP3A isoforms and P-gp was highly variable. CYP3A4, CYP3A5 and P-gp levels were significantly higher in CD than in control group.

Conclusion: Our results demonstrated changes in the duodenal and hepatic expression of CYP3A/P-gp in patients with CD before treatment. Further investigations, quantifying protein content and activity must be undertaken to understand how such changes affect drug absorption and bioavailability of drugs such as corticosteroids given for their treatment.

M19
Drugs dispensed to children in Sweden - national data and geographical differences

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Background: Aspects such as distance to healthcare providers, tendency to seek medical care and local tradition in treatment may influence drug use. In July 2005, a new national register with patient identity data from all prescriptions dispensed to the Swedish population was established. Data from this register can be used to estimate prevalence of drug use among children.

Aim: To compare purchase of drugs for children aged 0–14 yr in Sweden nationwide to the counties of Jämtland and Stockholm.

Methods: We compared the 6 month (July–December 2005) prevalence of drugs dispensed to children 0–14 yr of age in Sweden (9 million), Stockholm (1.9 million) and the county of Jämtland (130 000).

Results: In Stockholm 43.5% of the boys and 39.7% of the girls aged 0–4 yr had purchased a prescription drug compared with 40.8% and 37.2% respectively in Sweden. In Jämtland there were fewer, 34.2% of the boys and 29.9% of the girls. The difference was smaller among children aged 5–14 yr (both sexes) with 26.1% in Stockholm, 25.2% in Sweden and 21.6% in Jämtland. Dispensing of antibacterials to children 0–4 yr was greater in Stockholm, 221 per 1000 inhabitants compared with both Jämtland, 135 per 1000 inhabitants and Sweden as whole, 196 per 1000.

Conclusion: The percentage of children dispensed any prescription drug was greater in both Stockholm and Sweden than in Jämtland. Dispensing of antibacterials was more than 50% greater in Stockholm than in Jämtland for children aged 0–4 yr.

P1
Off-label and unlicensed prescribing: the perceptions of Australian doctors

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Background: Off-label (medicine used outside the terms of its manufacturer's product information [PI]) and unlicensed (medicine used without a manufacturer's PI) prescribing is common and widespread. It occurs most frequently within the paediatric population, however, it has been found to happen across all age groups. This study investigated the perceptions of doctors towards off-label (OL) and unlicensed (UL) prescribing.

Methods: Qualitative phase – individual interviews were conducted with a sample (46) of hospital physicians and general practitioners (GPs) from urban, rural and remote Australia. Three focus groups were held with participants from each area. *Quantitative phase* – a survey containing attitudinal, factorial vignette and demographic sections was sent to a national random sample of 1000 hospital physicians and GPs. Attitudinal and demographic data were summarised using descriptive statistics. Data from the factorial vignettes were analysed using analysis of variance and multiple regression within a hierarchical linear model.

Results: Qualitative phase – themes identified as being associated with OL and UL prescribing were setting, patient group, familiarity with the medicine, awareness about the OL or UL prescribing, and informing the patient. *Quantitative phase* – the useable response rate was 45%. Respondents comprised 77% GPs and 23% specialists. OL prescribing was perceived as appropriate by 56% of doctors. UL prescribing was regarded as appropriate by 29% of doctors and inappropriate by 45%, whilst 26% offered no opinion. Many doctors were uncertain about the legality of OL (28%) and UL (31%) prescribing. Young age of the patient (i.e. paediatric patients), unfamiliarity with the medicine and unaware that the prescription was OL or UL were perceived to present risks to the patient. Unfamiliarity with the medicine and being unaware that the prescription was OL or UL were regarded as unethical and inappropriate prescribing.

Conclusion: Greater education of doctors on the nature and legality of OL and UL prescribing is necessary in order to promote quality use of medicines.

P2
PGE_2-dependent proliferation and prostaglandin receptor signalling in growth plate chondrocytes

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Background: Prostaglandin E_2 (PGE_2) is synthesised by cyclooxygenases and play an important role in bone development and metabolism. The effects of prostaglandins are mediated by prostaglandin receptors (EP-1 - EP-4). We analysed the effects of different doses of PGE_2 on the proliferation of isolated growth plate chondrocytes of the rat. Furthermore, we studied the effects of prostaglandin receptor agonists and antagonists on the proliferation of growth plate chondrocytes. Finally, we detected EP-1 and EP-2 receptors as well as COX-1 and COX-2 in cultivated growth plate chondrocytes by immunocytochemistry and RT-PCR.

Methods: Chondrocytes were isolated from growth plates of 4 week old Sprague Dawley rats, cultured in 98-well-plates, stimulated with 18^{-6}, 10^{-7}, 10^{-8}, 10^{-9}, 10^{-10} M PGE_2 and with different EP receptor agonists and antagonists (10^{-6} M) for 24 h. As proliferation assays the semiquantitative dsDNA determination and [^{3}H]-thymidin incorporation were used. EP-1, EP-2, COX-1 and COX-2 expression were analysed immunocytochemically by the APAAP-method and by RT-PCR.

Results: Stimulation with PGE_2 triggers DNA synthesis in a dose dependent manner with a maximum at 10^{-8} M. EP-1/ EP-3 specific agonists and EP-1 selective agonists increased DNA-synthesis, whereas the effect of PGE_2 was suppressed by EP-1 selective antagonists. The expression of EP-1 receptors, COX-1 and COX-2 *in vitro* could be demonstrated by means of RT-PCR and immunohistochemitry.

Conclusion: PGE_2 stimulates the proliferation of growth plate chondrocytes *in vitro* in a dose-dependent fashion via the EP-1 receptor. These findings open new aspects for possible long term effects of cyclooxygenase inhibitors in children.

P3
Guidelines for off-label and unlicensed use of medicines: better prescribing, promoting better research, promoting better prescribing

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Background: Off-label and unlicensed prescribing is widespread in paediatric practice, with reported rates up to 90% in hospitalised patients. Such prescribing is not illegal and may sometimes be clinically appropriate, but is associated with a number of important clinical, safety and ethical issues. No explicit guidance has so far been available to assist clinicians in assessing appropriateness when considering such prescribing.

Methods: We describe the development of an explicit approach to guide clinicians, policy makers and funders of health care in systematically evaluating the appropriateness of medicines proposed for off-label or unlicensed use. Our consensus development process elicited input from a range of clinicians, a consultant in health ethics and law, and included consultation with hospital Drug Committees and the Department of Health in the state of New South Wales, Australia.

Results: Three broad categories of appropriate off-label/ unlicensed use are identified:
1. Use justified by high quality evidence
2. Use within context of a formal research proposal
3. Exceptional use, justified by individual clinical circumstances

Guidance on an appropriate process for informed consent is given for each category of appropriate off label/ unlicensed use. If there is no high quality evidence supporting such use, and the medicine is not suitable for exceptional or research indications, its use is generally not recommended. This will help reduce children's exposure to unnecessary risk.

Conclusion: Wider adoption of these guidelines should promote evidence-based prescribing, enhance patient safety, and stimulate more clinically relevant medicines research, which will in turn support better prescribing decisions and improved health outcomes in children.

P4
Pharmacokinetics and peak and trough concentrations of gentamicin in the neonate: a review of the literature

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Background: Treatment with gentamicin is essential in proven or suspected Gram-negative sepsis in the neonate. Several gentamicin therapeutic schedules have been reported to treat the neonate and they differ for the dose and for the interval between doses. Pharmacokinetic parameters of gentamicin have been measured in the neonate by different authors and these parameters range in a wide interval.

Aims: The aim of this study is to review the pharmacokinetics and the peak and trough concentrations of gentamicin in the neonate.

Results: The peak concentration between 5 and 10 µg/ml and trough concentration <2 µg/ml are considered optimal. Peak concentrations <5 µg/ml are non-therapeutic and peak concentrations >10 µg/ml and trough concentrations >2 µg/ml generate nephrotoxicity and ototoxicity. Gentamicin was administered to neonates with gestational age ranging from 23 weeks to term. The pharmacokinetic parameters of gentamicin vary within a wide range during neonatal development. In order to give an idea of the main kinetic parameters of gentamicin in the neonate we have calculated the clearance (Cl), the volume of distribution (Vd) and the half-life ($t_{1/2}$) using the data available in literature. We have also compared these data with those of the adult. The published data can be arranged into two groups namely "low birth weight neonates" with a body weight of 1,370$\pm$390 g and "term neonates" with a body weight of 2,988$\pm$713 g ($p<0.0001$). Cl (l/h/kg) is 0.044$\pm$0.02 (low birth weight) and 0.047$\pm$0.003 (term; P=0.503); in the adult it is 0.82$\pm$0.11. Vd (l/kg) is 0.55$\pm$0.28 (low birth weight) and 0.47$\pm$0.05 (term; *P*=0.205); in the adult it is 0.31$\pm$0.10. $t_{1/2}$ (h) is 11.7$\pm$8.26 (low birth weight) and 6.72$\pm$0.94 (term; *P*=0.039); in the adult it is 2–3 h. In low birth weight infants, the daily gentamicin dose used most frequently is 2.5–3 mg/kg. The dose of 3.5 mg/kg should require that the interval between doses be adjusted according to the gestational age. In term neonates, a gentamicin dose of 4 mg/kg every 24 h is preferred to the dose of 2.5 mg every 12 h. The former generates higher peak concentrations and lower trough concentrations than the latter.

Conclusions: The comparison of the pharmacokinetic parameters between "low birth weight infants" and "term infants" revealed that $t_{1/2}$ is double in the former compared with the latter whereas Cl and Vd values are similar in both groups. Cl is smaller in the neonate than the adult whereas $t_{1/2}$ and Vd are greater in the neonate than the adult. Gentamicin is mainly eliminated by the kidney and renal function is reduced in the neonate and this explains the longer $t_{1/2}$ and the lower Cl in the neonate compared to the adult.

P5
Idiopathic intracranial hypertension may be caused by reactivation of latent cerebral toxoplasmosis because of disturbances in t. gondii and/or host defense mechanisms

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Background: Idiopathic intracranial hypertension (IIH) presents with headaches associated with an increased cerebrospinal fluid pressure. Recently, we have demonstrated that recurrent headaches in non-HIV infected subjects were due to acquired cerebral toxoplasmosis (CT). The aim of this study was therefore to focus on the general pathomechanisms that may lead to reactivation of latent CT and manifest as IIH.

Methods: Literature data cited in this work were selected to illustrate that various factors may affect latent CNS T. gondii infection/ inflammation intensity and/or host defense mechanisms, i.e. the production of NO, cytokines, tryptophan degradation by indoleamine 2,3-dioxygenase (IDO), mechanisms mediated by an IFN-g responsive gene family, limiting the availability of intracellular iron to T. gondii, and production of reactive oxygen/nitrogen species (ROS), and finally cause choroid plexitis.

Results: Examples of various triggers revealing IIH and accompanying disturbances of IFN-g-mediated immune responses that control T. gondii, are presented in the Table.

Carbamazepine	Increased kynurenic acid synthesis and activity of kynurenine aminotransferase. Decreased NO production
Ciprofloxacin	Increased IL-2 and IFN-g mRNA concentrations
Beta-lactam antibiotics	Increased CD4+ and CD8+ T-cell-mediated immune responses in several patients
Iron deficiency anaemia	Increased TNF-a, IL-6 levels. Oral iron therapy caused resolution of IIH. Iron decreased NO production
Nitrofurantoin	Increased ROS production. Redox reactions regulate IDO and tryptophan metabolism along the kynurenine pathway as IDO is a unique enzyme in that it can utilise superoxide anion radical as both a substrate and a co-factor

Conclusion: Subjects with IIH should have tests for T. gondii infection obligatorily performed.

P6
Therapeutic drug monitoring of pentobarbital in paediatric status epilepticus patients

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Background: Paediatric patients with status epilepticus refractory to benzodiazepines and phenytoin can be treated with pentobarbital. Guidelines for inducing and maintaining adequate plasma pentobarbital levels (20-40 mg/L) have been published but are not based on data obtained in children. Furthermore, pharmacokinetic studies in adults demonstrated considerable variability between patients. The aim of this study was to evaluate whether therapeutic drug monitoring (TDM) can be useful to optimise pentobarbital therapy in paediatric patients.

Methods: Fifty-nine pentobarbital plasma concentration data were available from 8 patients (age: 7 months-12 y). Individual pharmacokinetic parameters were derived by Bayesian analysis using the pharmacokinetic software program MW-Pharm. The following population three-compartment pharmacokinetic parameters were used; Vd: 0.037±0.015 l/kg, Kelm: 2.17±1.53 h^{-1}, k12: 21.3±14.6 h^{-1}, k21: 4.8±3.0 h^{-1}, k13: 4.5±3.4 h^{-1}, k31: 0.26±0.11 h^{-1}. The latter parameters were assessed in patients (age: 4–52 yr) receiving continuous intravenous thiopental infusions[1]. For each patient in the present study the measured pentobarbital plasma concentration(s) and the population model were used to predict the subsequent measured concentration. The predicted pentobarbital concentration was compared with the actual concentration. This process was repeated for every measured pentobarbital concentration available which is comparable to the clinical situation in which TDM is performed.

Results: The individually predicted plasma concentrations of pentobarbital correlated well with the measured concentrations. Bias was 2.5% (–4.2, 9.2%; 95% confidence interval, *n*=51) and precision was 25% (13, 33%; 95%CI).

Conclusion: TDM can be useful for maintaining adequate pentobarbital levels in paediatric patients.

Reference

1. Touw. Pharm Weekbl 1991;126:959.

P7
First results of nestin synthesis in granulation tissue of infants and adults – new insights for wound healing

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Background: Nestin is an intermediate filament abundantly synthesised in the developing central nervous system and somites in embryonic stage. Actual analysis indicated nestin as a marker for angiogenic endothelium in tumour vasculogenesis. In the present study we investigate the synthesis of nestin in endothelium of granulation tissue of adults and infants to test whether nestin is a specific marker for tumour angiogenesis.

Methods: Granulation tissue from wound edges of adults (*n*=5) and infants (under 3 months, *n*=5) were analysed by immunostaining with a polyclonal antibody (1:200 and 1:1000) with automated staining methods according to standardised methods. As controls normal breast tissue were stained.

Results: Granulation tissue from adults showed a moderate to strong synthesis of nestin in newly formed vessels especially in capillaries, whereas greater vessels only occasionally synthesise nestin and to a markedly lesser extent. Granulation tissue of infants showed a very strong nestin synthesis even if a five fold lower antibody concentration is used. In the control tissue nestin could be found occasionally in a weak intensity of capillaries.

Conclusions: Nestin is synthesised in granulation tissue and therefore is not specific for tumour angiogenesis. Nestin is present in newly formed capillaries and to a lesser extent in greater vessels so that it could function as a marker of proliferating endothelial cells. The tremendous nestin synthesis in granulation tissue from infants indicates the difference in wound healing of the growing body. Further investigations of the function and regulation of nestin in proliferating endothelium is needed.

P8
Orphan drugs in treatment of inborn errors of metabolism: status quo after six years of European orphan medicinal product legislation

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Background: European orphan medicinal product legislation was developed to offer patients with rare diseases the option of high quality drug therapy. Generally inborn errors of metabolism (IEM) are "orphan diseases" (prevalence <5:10 000) per definition. Unfortunately, drug therapy for many of these conditions is inadequate. Six years after initiation of the orphan drug regulation programme we investigated its contribution to substantial improvement of treatment of IEM.

Methods: We reviewed all orphan drugs for IEM approved since 2000 using the European Public Assessment Report (EPAR) and scientific reference databases. Ongoing clinical trials have been compiled based on official registers and available information from the pharmaceutical industry.

Results: Between March 2000 and January 2006 eight orphan drugs for seven metabolic diseases have reached EC market approval. No (1/7) or only unsatisfactory (6/7) therapeutic alternatives have been available before. The prevalence of indications (48 to 25 800 patients in the EU), and subsequently the quality of data available at market approval, differed substantially between the particular drugs. Studies including 16 up to 1300 patients with a maximum follow up of 6 to 108 months resulted in favourable risk/benefit ratios. Seven drugs however received market authorisation under exceptional conditions, due to insufficient data.

Conclusion: European orphan drug legislation opened safe and effective treatment to a considerable number of patients with potentially life-threatening and disabling diseases. However, the ultimate goal to improve drug therapy in orphan diseases (e.g. IEM) requires treatment of the majority of index patients in prospective clinical trials.

P9
Liquid vitamin E for children – which product?

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Background: Vitamin E is used in premature babies, infants and children with liver diseases. Pharmacies rely on extemporaneous production or import of non-approved products, as no suitable product is marketed in Norway. Inquiries from pharmacies to Drug Information Centres indicate uncertainties regarding formulation and which product to hand out to patients. Two formulations are available: one for veterinary use and one intended for premature babies. The formulation for veterinary use is called "Vitamin E50 mg/ml drops vet" which contains dl-α-tocopheryl acetate, polysorbate and ethanol. It is not intended for human use and is clearly marked "Medicine for animals" with dosing information for several animal species on the label. There are indications that polysorbate may contribute to necrotising enterocolitis in babies. The ethanol content is 200 mg/ml. If administered to premature infants, the standard dose corresponds to an ethanol intake of 60 mg 96% ethanol. If given to a baby with a birth weight of 1000 g, this equals one centilitre 45% alcohol for a 70 kg adult. The other formulation is called "Vitamin E50 IE/ml drops for premature babies". It contains tocophersolan and was formulated to avoid polysorbate and ethanol. The name indicates approval for paediatric use, but no data or approvals support this. There are extremely few data on equivalent dosages or serum concentrations of vitamin E after intake of tocophersolan in premature or full term neonates. Children with biliary stasis and vitamin E deficiency needed dose reductions by 83% (64.3-93.5%) compared to dl-α-tocopheryl acetate.

Aim: The aim of this study was to investigate which liquid vitamin E is procured for patients by Norwegian hospital pharmacies.

Methods: A questionnaire was sent to all hospital pharmacies in Norway (n=30), asking them if they had procured liquid vitamin E since 1st January 2003. If they did, information about type of formulation, active ingredients and excipients, product name, strength, and origin of formulation recipe or product were recorded.

Results: 27 (90%) of 30 hospital pharmacies answered the survey. 18 (66.6%) had procured vitamin E drops, either by own production or by buying from others. 11 pharmacies (40.7%) had procured a product similar to Vitamin E 50 mg/ml drops for veterinary use. Some pharmacies confirmed that this product has been given to paediatric patients. Nine pharmacies (33.3%) had procured a product similar to Vitamin E 50 IE/ml drops for premature babies, the majority by own production at the pharmacy lab. The product went by two different names: "Vitamin E 50 mg/ml drops" and "Vitamin E 50 IE/ml drops for premature babies", despite being made according to the same formulation recipe. Four hospital pharmacies included the dosage for premature babies receiving oxygen therapy on the label. Six pharmacies mentioned premature children on the label, either as part of the product name or in dosing information, while two pharmacies did not mention premature children. Strength was declared either as 50 mg/ml (seven pharmacies) or as 50 IE/ml (two pharmacies). No hospital pharmacies reported any use of imported products.

Conclusion: Data on different formulations, concentrations and optimal dosing is not consistent, and practice varies between pharmacies. Lack of consensus may cause confusion, errors, sub-optimal treatment, adverse reactions or overdosing in children. This survey revealed the need for guidelines on vitamin E formulations.

P10
Impact of a paediatric vial on the magnitude of systematic medication errors in neonates

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P11
Levetiracetam pharmacokinetics in neonates at birth

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Background: Plasma elimination half-life of levetiracetam is 6 to 8 h in adults, 5 to 7 h in children and increases to 10-11 h in healthy elderly volunteers while the distribution volume of this drug is 0.5 to 0.7 L/kg. Pharmacokinetic observations in neonates have not yet been reported but Johannessen et al assumed rapid elimination based on low levetiracetam concentrations observed at the postnatal age of 3 to 5 days in 6 breast-fed neonates[1].

Case reports: Following elective Caesarean, two healthy neonates (2,700 and 2,960 g) were born. Pregnancy was uneventful but the mother was treated with levetiracetam (2 x 1500 mg/day, Keppra® UCB Brussels, Belgium) because of complex partial epilepsy. The time interval between the last administration of levetiracetam and delivery was about 45 minutes.

After informed consent of both parents, amniotic fluid samples, umbilical cord blood and venous blood were collected up to 36 h of postnatal age (0, 10 and 25 h in the first and 0, 10 and 36 h in the second neonate). Levetiracetam in amniotic fluid was 32.3 and 30.8 µg/ml. Based on visual inspection of the time-concentrations profiles, estimated plasma elimination half life ($t_{½}$) of levetiracetam was 16 to 18 h in neonates.

Conclusions: Based on repeated blood sampling in a formula-fed twin, the estimated serum elimination half life of levetiracetam at birth is 16 to 18 h.

References

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P12
A comparison of industry sponsored and investigator initiated trials in children before and after the 12th amendment of German drug law

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Background: In August 2004, European Directive 2001/20/EG, which should facilitate research including minors, was implemented into German drug law. This 12th amendment of German drug law yields high regulatory standards. Industry-independent researchers could have difficulties to fulfil these excessive formalities. Therefore, one of the effects could be a reduction of investigator initiated trials. To ascertain whether the number of investigator initiated trials, especially with minors, has decreased data about the number and the quality of trials conducted according to German Drug law.

Methods: Applications to the IRB of the University of Ulm of the last six years have been analysed to determine trials including minors. A ratio of investigator initiated trials vs industry sponsored studies was determined and compared using Fisher's Exact Test.

Results: Although the overall number of applications including minors as research subjects has increased at Ulm University, the number of clinical studies conducted according to German drug law has not increased. The investigator initiated trials have decreased compared to industry sponsored studies ($P<0.05$).

Conclusion: In contrast to the aim of the lawgiver, the new regulatory directives might lead to a decrease in investigator initiated trials in children. Trials without benefit for industry, e.g. trials comparing different medications or trying to optimise therapy regimens, would be omitted. Academic research for the benefit of children could depend more and more on third party funds in the future.

P13
St John's wort – evidence based alternative for the treatment of juvenile depression? An overview on indications, evidence and prescribing patterns

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Background: Antidepressant therapy in childhood and adolescence is difficult since strong warnings for the use of serotonin-reuptake-inhibitors (SSRIs) have been issued by regulatory authorities worldwide. The risk-benefit ratio of SSRIs seems to be unfavourable for minors and emphasises the need of pharmacotherapeutic alternatives to SSRIs. In Germany, St John's wort (SJW) is labelled for minors up to 12 y and could be a therapeutic alternative.

Methods: We reviewed indications, effectiveness and safety and examined prescribing patterns of SJW in Germany. We performed a retrospective analysis of a health insurance sample, representing prescriptions for 27% of all children aged 0 to 16 yr.

Results: In literature there are weak indications for effectiveness of SJW in childhood and adolescence. Long term safety data and data of side-effects are missing. Our prescribing data suggests a small but relevant off-label use of SJW in minors. Composed products may have more side effects than pure extracts of SJW. They are prescribed even for very young children.

Conclusion: There is no evidence for treatment of mood disorders in childhood and adolescence with SJW.

P14
Modelling using NONMEM and Bayesian estimator in renal graft children

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Background/Aims: Cyclosporin A (CsA) is an immunosuppressive drug used in renal graft. Important interindividual pharmacokinetic (PK) variability and narrow therapeutic index make its monitoring necessary. We developed a PKpop model with identification of CsA variability factors allowing a Bayesian estimation of individual AUC in stable paediatric renal transplant patients.

Methods: A population PK approach was realised using NONMEM to study 256 CsA PK profiles (98 renal graft children: mean age 9.7 ± 4.5 yr). A two compartment model with an Erlang distribution and a first order elimination was chosen for its superiority on zero, first order and Weibull distribution models in adults. Bayesian estimation was made on the basis of three blood concentrations taken in the first 4h post dose.

Results: The final model included the influence of weight and post transplant delay on both apparent central volume of distribution and clearance in an increasing way. Bayesian estimation allowed accurate prediction of $AUC_{0\text{-}12h}$ using predose, C1h and C3h blood samples with a mean bias between observed and estimated AUC of 0.5% and a good precision (RMSE = 10.9%).

Conclusion: Factors identified to influence CsA PK interindividual variability are easy to collect in routine course, allowing the use of this model in clinical investigational studies.

P15
A limited sampling strategy to estimate individual pharmacokinetic parameters of MTX in children with acute lymphoblastic leukaemia

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Background: Acute lymphoblastic leukaemia (ALL) in paediatrics is a largely curable disease (80% 5 year survival). Routine methotrexate (MTX) monitoring is employed during high doses MTX (HD-MTX) for folinic acid rescue adaptation. In the present study we estimated population pharmacokinetic parameters of MTX in children with ALL and developed a limited sampling strategy for monitoring.

Methods: 79 children with ALL were enrolled at diagnosis in the European chemotherapy protocol EORTC 58951. Blood samples before and at 24, 48 and 72 h after the beginning of infusion as well as patient characteristics were collected. Plasma MTX was determined by an enzyme multiplied immunoassay technique (EMIT). Pharmacokinetic analyses were performed on 301 MTX courses from 61 children using NONMEM (Version 5.1). A two compartment structural model was selected. Pharmacokinetic parameters were validated on 18 children.

Results: Mean pharmacokinetic parameters were: CL = 9.4 L/h (CV = 25.5%), V_1 = 27.7 L (CV = 23.7%), k_{12} = 0.0200 h^{-1} (CV = 27.7%) and k_{21}= 0.0608 h^{-1} (CV = 14.4%). The two sampling schedule (24 and 48 h) combined with pharmacokinetic parameters, allowed one to predict the time at which folinic acid administration could be stopped.

Conclusion: Using a population approach, we evaluated intra-individual pharmacokinetic variability of MTX. A limited sampling strategy was developed to determine individual pharmacokinetic parameters, reduce HD-MTX monitoring sampling and hospitalisation duration.

P16
LC-MS determination of lamotrigine and its metabolites in plasma for study of mechanisms for the pharmacokinetic variability of lamotrigine in connection with pregnancy and in the neonatal period

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Background: The aim of this work was to develop a method for simultaneous quantification of lamotrigine (LTG) and three of its metabolites in human plasma for studying the influence on pharmacokinetics observed in connection with pregnancy and the low capacity in the neonates to eliminate LTG. If decreased LTG concentrations during pregnancy are due to induction of the LTG metabolism, it will result in an altered ratio between the metabolites and LTG in plasma.

Methods: The samples are deproteinised with acetonitrile. The method utilised chromatographic separation by a reversed-phase column and gradient elution, and mass spectrometric detection with monitoring of the positively charged molecular ions. Two internal standards were used for quantification, a structural analogue of LTG, and a deuterated analogue of a morphine-3-glucuronide. Fifty-five randomly selected clinical samples were used for validation.

Results: Concentrations of LTG and the 2-N-glucuronide were detected. The median ratio LTG-2-N-glucuronide/LTG

was 0.11 (range, <0.01–0.64). In patient samples LTG-2-N-methyl and LTG-2-N-oxide were typically not detectable. Using this method, the coefficient of variation is less than 5% for lamotrigine and less than 16% for N-2-glucuronide. The limits of detection were between 0.05 and 0.16 µmol/l. The comparison performed between routine HPLC-UV and LC-MS displays good correlation (r^2= 0.91).

Conclusion: The presented procedure is a rapid method involving a low plasma volume for simultaneous quantification of LTG and three of its metabolites, lamotrigine-2-N-glucuronide, lamotrigine-2-N-methyl, and lamotrigine-2-N-oxide. The method is suitable for investigation of alteration in pharmacokinetics of LTG in pregnancy and during the neonatal period.

P17
Oral vitamin E therapy for children – do we need guidelines?

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Background: Vitamin E therapy is common in children in various ages and diseases, such as, cholestatic liver disease, malabsorption disorders, and chronic diseases. Premature babies and sick infants are treated with oral vitamin E therapy in association with oxygen therapy. However, health personnel may consider oral vitamin E to be a nutrient supplement rather than a therapeutic drug, which may impact drug therapy. Little distinction between therapeutic treatment, correction of deficiency and precautionary supplementation seem to exist. Some recommendations for oral therapeutic use of vitamin E can be found, but the optimal dose for the different indications and compounds is not well established. A variety of dosages and product properties may result in unpredictable variations in therapy.

Purpose: To review published data on oral vitamin E therapy, and obtain all available information of clinical use of different preparations, type of vitamin E, dosage, toxicity and adverse drug reactions in relevant patient groups.

Methods: Literature search in Medline, data from Cochrane and Micromedex® databases, product monographs and other relevant articles and textbooks, such as British National Formulary for Children, Medicines for Children, and Pediatric Dosage Handbook.

Results: Vitamin E therapy has been used in a number of established or experimental indications, including premature infants, neonates with growth retardation and low birth weight, liver or bile disease, paediatric obesity-related liver dysfunction, cystic fibrosis, abetalipoproteinaemia, beta-thalassaemia, sickle cell disease, inborn errors of metabolism, epidermolysis bullosa, glucose-6 phosphate dehydrogenase deficiency, and focal segmental glomerulosclerosis. However, few randomised clinical trials on oral therapeutic use of different vitamin E compounds in children have been done. The vitamin E compounds used in published studies include alpha tocopheryl acetate, alpha tocopherol and tocophersolan, but the name of the specific compound is sometimes omitted, and may be unspecified on physicians' prescriptions. The biological activity varies among the different compounds, and this may not be taken into consideration when new vitamin E compounds are introduced. Additionally, tocophersolan may have considerably higher bioavailability compared to other tocopherols, which may impact dosing recommendations to large dose reductions in some patients. The safety profile of various vitamin E compounds has not been examined systematically in paediatric patients, but a possible toxic serum level of 3.5 mg/dl has been identified in neonates. Safety issues arise from use of excipients such as polysorbate, alcohol, and polyethylene glycol. Lack of comparable, systematic studies for dose and choice of compound makes the interpretation of data difficult.

Conclusion: There is a need to review oral vitamin E therapy in neonates and children. The relationship between bioavailability, effect, and dosage of vitamin E is not clear, and dosing recommendations vary in literature. Further studies are needed, so that active ingredient, dosing and efficacy in various ages and disease states can be established. Guidelines for paediatric use of oral vitamin E are therefore needed.

P18
Use of antidepressants in children and adolescents in Sweden

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Background: The efficacy of fluoxetine in 12–17 yr old depressed patients is well documented. Signals of possibly suicide related behaviour have, however, caused authorities to warn against use of antidepressants (AD) in these ages.

Aim: To investigate the current prevalence of AD use in children and adolescents in Sweden (1.7 million inhabitants 5–19 yr of age).

Methods: Individual data on prescriptions dispensed at all pharmacies were obtained from the Swedish Prescription Registry for July–December 2005.

Results: In children 5–9 yr of age, 124 were dispensed AD corresponding to a point prevalence of 0.23 per 1000 inhabitants. In 10–14 yr olds, 797 boys and 689 girls were dispensed AD; point prevalence 2.5 and 2.3 per 1000 inhabitants, respectively. In 15–19 yr of age, 2716 boys and 5754 girls were dispensed AD; point prevalence 9.2 and 20.1 per 1000 inhabitants.

Discussion: A recent review estimated the prevalence of depressive disorder in these age groups as 0.8% in 8–9 yr olds, to 1.8 – 5.0% after puberty, with equal sex distribution before puberty and twice as many women as men thereafter. Assuming the prevalence levels of 0.8, 1.5, and 5.0% in the age groups 5–9, 10–14, and 15–19, our results suggest that the drug treated portion of the depressed adolescents were 3%, 16%, and 29%.

Conclusion: Only a minor fraction of depressed children and adolescents receive antidepressant medications in Sweden. Hopefully the remaining individuals are receiving effective psychosocial interventions.

P19
Global variation of PD associated peritonitis in children: a report of the International Pediatric Peritonitis Registry (IPPR)

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Background: Peritonitis is a major complication of chronic peritoneal dialysis (PD). Guidelines for the empirical therapy of PD associated peritonitis were published by an international expert committee in 2000.

Methods: The web-based IPPR with 43 participating paediatric centres from 14 countries in three continents collected data on a 501 peritonitis episodes from 2001 to 2004.

Results: Culture negative peritonitis (CNP) was rarest in North America (11%) and Argentina (15%), whereas CNP accounted for 42% of all episodes in Turkey and 67% in Mexico (overall rate 29%, heterogeneity among countries $P < 0.0001$). Of the episodes where an organism was cultured, North America (48%) and Argentina (70%) had the highest rate of Gram negative episodes (overall rate 36%). *S. aureus* was predominant in Mexico (44%), whereas the rate of *S. aureus* in other countries ranged from 15% to 22% ($P < 0.0001$).

The guidelines recommend empirical antibiotic therapy with ceftazidime and either a first generation cephalosporin or a glycopeptide. While there was no significant regional variation in susceptibility of organisms to ceftazidime (62%–81%), sensitivity to first generation cephalosporins ranged from 80% in Eastern Europe to 30% in North

America ($P < 0.005$). Glycopeptide sensitivity of Gram positive organisms was below the average rate of 95% in Eastern Europe (89%) and Turkey (89%). There was considerable variability in the susceptibility of *S. aureus* to methicillin, ranging from 32% in Turkey to 100% in Argentina.

Conclusion: Pronounced regional variation exists for the rate of culture negative peritonitis, distribution of causative organisms and antibiotic susceptibilities. This information will have a major impact on the formulation of revised guidelines for empirical therapy of PD-associated peritonitis, which must take into account the local spectrum of causative organisms and antibiotic susceptibilities.

P20
Antibiotic treatment of peritonitis in children: a report of the International Pediatric Peritonitis Registry (IPPR)

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Background: Peritonitis (P) is the primary factor compromising long-term peritoneal dialysis (PD) therapy and its optimal therapy remains uncertain.

Methods: Following the publication of Consensus Treatment (tx) Guidelines in 2000, in which empirical therapy was stratified by disease severity to a 3rd generation cephalosporin for all patients plus a 1st generation cephalosporin for low-risk and a glycopeptide for high-risk patients, the web-based IPPR was established to evaluate safety and efficacy of the guidelines following their implementation in 43 paediatric centres from 14 countries.

Results: A total of 491 episodes of peritonitis were entered into the registry. Conformance to empirical tx guidelines occurred with 61% of episodes. Staphylococcal organisms were the most frequently cultured, and culture negative peritonitis represented 0-65% of episodes by centre. *In vitro* evaluation revealed 71% and 81% organism sensitivity to the low and high risk tx, respectively, in each case inferior to the results with aminoglycosides. Resistance to empirical tx was associated with an odds ratio (OR) for poor day 3 response of 3.24 (P=0.01) with low risk tx and 3.8 (P=0.01) with high risk tx. The OR for poor early response was 4.6 (P=0.0002) for intermittent vs continuous empirical tx. Subsequent guideline recommended modification of therapy occurred in 83% of cases. Overall, 92% of cases achieved remission, a portion following relapsing peritonitis (8%) and catheter exchange (6%). Incomplete final recovery was predicted by a poor day 3 response.

Conclusions: These data serve as the basis for new evidence based guidelines. Modification of empirical therapy recommendations to include aminoglycosides should be considered.

P21
Sirolimus-based immunosuppression vs cyclosporin minimisation in paediatric patients with cyclosporin induced nephrotoxicity: 2 year data

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Background: It is unclear whether sirolimus (SRL)-based immunosuppression or cyclosporin (CsA) is superior in patients with chronic CsA-induced nephrotoxicity as a major component of chronic allograft nephropathy (CAN).

Methods: We therefore conducted a 24 month case control study in 22 paediatric renal transplant recipients with declining graft function due to biopsy-proven CsA-induced nephrotoxicity, investigating the efficacy and safety of an SRL-based immunosuppression, combined with mycophenolate and steroids *vs* CsA minimisation (–39 ± 8.9%) over comparable post transplant periods.

Results: Although the SRL group had a lower baseline GFR and a higher proteinuria, indicative of a more pronounced CAN, graft function improved or stabilised after switch to SRL in a number of patients (12/13; 92%) comparable to that of the CsA minimisation group (8/9; 89%). In both cohorts the median increase of GFR after 1 year persisted in the 2nd year of observation. In patients exhibiting no borderline changes at the time of study entry, switch to SRL was safe. Under SRL therapy, 46% of patients developed hypercholesterolaemia and 62% hypertriglyceridaemia; three out of 13 recipients (23%) required statin therapy; 38% needed erythropoietin administration due to hypogenerative anaemia. Proteinuria was found to be aggravated in 46% of SRL-treated patients, but no recipient experienced de novo proteinuria.

Conclusion: Both therapeutic strategies for CsA nephrotoxicity, CsA withdrawal and SRL-based therapy or CSA dose reduction, led to a comparable relative and absolute improvement of graft function over a 2 year period. These two strategies should be compared in a prospective randomised study.

P22
Recurrent headache as the main symptom of acquired cerebral toxoplasmosis in non-human immunodeficiency virus-infected subjects with no peripheral lymphadenopathy

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Background: Headache, a frequent problem in medical practice, is also one of the most common clinical manifestations of acquired T. gondii infection of the central nervous system (CNS) in immunosuppressed subjects. This aim of this study was to present clinical and laboratory data of subjects with latent chronic cerebral toxoplasmosis (CT), who have been treated as apparently immunocompetent persons.

Methods: The patient population consisted of 11 children aged 7–15 yr (eight girls, three boys) and 1 adult woman hospitalised because of recurrent headaches, who had no enlargement of the peripheral lymph nodes.

Results: In 7 patients, the mean serum IgG Toxoplasma antibodies concentration was 189 ± 85 (SD) IU/ml (range 89–300 IU/ml), and in five other subjects, the mean indirect fluorescent antibody test titre was 1:829 ± 1:1360 IU/ml (range 1:40–1:5120 IU/ml, n = 16 tests, normal value = < 1:10 IU/ml). The complement fixation test was negative in Pt 1, while in Pts 2-4 the titre ranged from "±" to 1:10 IU/ml. The Sabin-Feldman test was in Pt 1 at first negative but after two weeks it increased to 1:200; in Pt 2 the titre was 1:50 and after 2 months it increased to 1:100 IU/ml. The agglutination test was in Pt 1 at first negative but it became positive after the next 3 weeks (1:20), while in Pt 2 the titre was 1:40 IU/ml. The immune studies performed in Pts 5–9 showed a decreased percentage of T lymphocytes, increased total number of B lymphocytes and serum IgM concentration, and impaired phagocytosis.

Conclusions: In non-HIV-infected subjects, chronic latent CNS T. gondii infection/inflammation may result in marked immune abnormalities. CT should be considered in apparently immunocompetent patients with recurrent headaches.

P23
Antibiotic prescriptions in the outpatient paediatric population

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Background: Antibiotics are widely prescribed for children and often their use is not rational (e.g. in viral infections). A literature review was performed with the

aim to evaluate antibiotic prescriptions in the outpatient paediatric population and to compare intra- and inter-country prescribing patterns.

Methods: A search was performed in the EMBASE and MEDLINE databases to identify pharmacoepidemiological studies published between 2000 and 2005 on antibiotic prescriptions in outpatient paediatric populations. A manual search of references was also performed.

Results: A total of 108 papers were retrieved, 32 of which were pertinent, but only 20 reported comparable data (prevalence and/or prescription rate). A total of 10 countries were involved in the studies. Prevalence varied from a minimum of 14.2% to a maximum of 71.8%, and the prescription rate from 0.2 to 2.2 prescriptions/person/year. Infants were the age group with the highest exposure to antibiotics. Inter-country quantitative and qualitative differences in antibiotic prescribing were observed: prevalence was higher in Italy and Canada and lower in the Netherlands and the UK. Penicillins were the most prescribed antibiotic class everywhere; cephalosporins were widely prescribed in Italy while their use is nearly negligible in Denmark and UK.

Conclusion: Wide differences were found in antibiotic prescribing between countries. Educational and regulatory interventions directed at physicians, pharmacists and parents/patients should be planned for improving the rational use of antibiotics. Moreover, an international collaborative epidemiological study should be planned to monitor the use of antibiotics in the paediatric population.

P24
Analgesic drugs for paediatric needs

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Background: Pain is a stressful event, often unrecognised and untreated in children, especially in the youngest ones. During 2005, the EMEA addressed the issue of the paediatric pain treatment and identified 14 potentially key drugs. An evaluation of the concordance between this statement and the available evidence was performed.

Methods: A literature search was performed in the Medline and Embase databases to retrieve RCTs concerning pain treatment in children. The RCTs involving the drugs identified by the EMEA were selected and evaluated. Moreover, an evaluation of the availability of the drugs on the market and of their licensing status in Europe (in particular in Italy, France and United Kingdom) was made.

Results: A total of 12,009 RCTs regarding paediatric pain treatment were found, 30% of which involved the 14 analgesic drugs identified in the EMEA document. There were wide differences in the number of studies available on each drug. Morphine was the analgesic with the highest amount of paediatric RCTs (>100); while dipyrone only had one. Only 8 of the 14 drugs are licensed for pain treatment in childhood in Italy, France and UK; in these countries clonidine does not have pain treatment among its indication.

Conclusion: Apart from a few, widely studied drugs (e.g. morphine), there is still scant evidence concerning the treatment of pain in children. Moreover, the differences in the licensing status in Europe underline the need for a European paediatric formulary in order to harmonise the indications and reduce discrepancy in access to evidence-based therapies.

P25
Biological disease modifying anti-rheumatic drugs (DMARDs) for children and adolescents according to the new Swedish National Prescription Register

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Background: Biological disease modifying anti-rheumatic drugs (DMARDs) have recently become increasingly important in the treatment of rheumatic and autoimmune disease in adults. Paediatric studies are emerging, but still little is known about the value and safety of these drugs when used in children and adolescents. All but one (etanercept) of the biological DMARDs lack paediatric labelling in Sweden. As a consequence, it is conceived that there is a substantial *off-label* prescription of these drugs to paediatric patients, but the dimension of the phenomenon is not known.

Objective: To describe the paediatric prescribing (0–19 yr, 2 158, 000 inhabitants) of the biological DMARDs adalimumab, etanercept, infliximab and rituximab in Sweden.

Methods: Data on prevalence of paediatric patients receiving biological DMARDs were collected from the newly established Swedish National Prescription Registry for July – December 2005.

Results: DMARDs were prescribed to 355 children and adolescents 0–19 yr: 13 children 0–4 yr, 28: 5–9 yr, 130: 10–14 yr and 184: 15–19 yr, with a prevalence of 3/100 000 in children 0–4 yr, 6/100 000 in 5–9 yr, 21/100 000 in 10–14 yr and 32/100 000 in 15–19 yr, respectively. The diagnoses for which these drugs are prescribed are not known from the register. Also, this analysis is potentially biased by the fact that expensive drugs are sometimes ordered directly to the in-patient clinic, where patients receive them without prescription.

Conclusion: The newly established Swedish National Prescription Register offers an opportunity to study paediatric use of the biological DMARDs with restrictions as described above.

P26
Drugs and birth defects – a Swedish information source on the Internet

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Background: Approximately one third of pregnant women report intake of drugs, vitamins or herbal medicines during early pregnancy. Consequently questions concerning fetal risks connected with medications are common.

A frequent issue is when a woman used medications prior to knowledge of her pregnancy. Another example is when physicians consider initiating or changing drug treatment in pregnant women. Available information within this area is often inconsistent and difficult to use for recommendations in clinical practice.

Methods: The information source "Drugs and Birth defects" – accessible on the non-commercial web site www.janusinfo.se – offers assessments on potential risks for the unborn child linked to maternal drug exposure during pregnancy. The information is intended for health care professionals and is easily used at point-of-care.

Each document consists of a short assessment of the drug followed by a survey on available data. The contents are based on data from the Swedish Medical Birth Registry and scientific literature. About 1,000 substances, all drugs on the Swedish market, are covered. The database is updated at least once a year. Authors are Bengt Källén and Karin Källén, from the Tornblad Institute, Lund University.

Results: "Drugs and Birth defects" has around 3400 hits per month, a number that is steadily increasing. Questionnaires indicate that most of the specialists are aware of the database and that 94% of the users consider the information being of great value.

Conclusions: An internet-based information source providing clinically usable assessments on fetal risks associated with medication during pregnancy is an appreciated tool in the every day work of health care professionals.

P27
SFINX - a database to reduce adverse drug reactions due to drug interactions

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Background: Drug drug interactions (DDIs) are a common and often preventable underlying cause for adverse drug reactions (ADRs). Extensive information flow about DDIs raises problems for clinicians to handle interactions.

Objective: The aim was to construct and update a DDI database (SFINX = SwedishFinnishINteractionX-referencing) as a common project between Sweden and Finland.

Methods: The database and data entering tool was built. Standard operation procedures (SOP) were created to standardise literature search strategies. Interaction texts were structured and classified. Data fields for connecting the information within SFINX to drug registries in both countries were identified and quality assured.

Results: An SQL database and administrative tool were constructed using Extensible Markup Language (XML). The literature SOP defines eight different literature sources, relevant search terms and strategies for each source. Additional data tools assure linkage of SFINX to the various drug registries. Warning texts divided into consequence, recommendation, mechanism and background are written by pharmacists and physicians and approved by clinical pharmacologists. Texts are classified regarding clinical relevance and level of documentation. The first version of SFINX included information on 4300 DDIs to be updated every three months. A web-based system is used in Finland by physicians and pharmacists to check patients' medication lists. The website had 5000 hits from health care professionals daily during the first weeks. SFINX is currently being installed in journal systems and pharmacy systems to create automated real-time warnings on DDIs.

Conclusion: SFINX is a valuable tool to deliver information on DDIs during drug prescribing and dispensing to prevent ADRs and improve quality of prescribing.

P28
Pregnancy outcome of women exposed to azathioprine during pregnancy: a prospective multicentre international study

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Background: Azathioprine (AZP) is widely used as chronic treatment for various autoimmune diseases or following organ transplant. AZP interferes with nucleic acid synthesis, and is teratogenic in animals. In view of the paucity of information on the use of AZP during pregnancy we investigated this subject in a prospective multicentre study. The primary objective was to determine whether AZP increases the risk for major malformations. The secondary objective was to compare the rates of spontaneous and therapeutic abortions, mean gestational age and weight at birth in pregnancies exposed to AZP.

Study design: This was a prospective, controlled, observational study. Pregnant women who contacted one of six teratogen information services in Israel, Canada and Europe to obtain information about the potential risks of AZP during pregnancy were enrolled in the study and followed-up after delivery. The outcome was compared to a cohort of pregnant women, who contacted the teratogen information centres for various reasons, but who did not take teratogenic drugs during their pregnancy.

Results: Follow-up was completed on 189 women in the AZP group and compared to information obtained on 246 women in a control group. The rate of major malformations did not differ between the exposed group and the controls, but the mean birth weight and gestational age were lower [2995 g vs 3252 g P=0.001) and 37.8 w vs 39.1 w (P=0.001), respectively]. The exposed group had relatively more cases of prematurity [21.4% vs 5.2% (P<0.001)] and low birth weight [23% vs 6.0% (P<0.001)]. The rate of spontaneous abortions was lower in the exposed group [1.7% vs 7.7% (P=0.006)].

Conclusions: These results suggest that AZP is not teratogenic during pregnancy; however, larger studies are needed to confirm this observation.

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Young misusers of hormonal pharmaceuticals: age dependent misuse pattern according to self-reports

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Background: Our Anti Doping Hot-Line works to discover, counteract and prevent the misuse of doping agents and its consequences in Sweden. The most common reported adverse events (AEs of illicit hormone pharmaceuticals-mostly anabolic androgenic steroids (AAS): acne, dyslipidaemias, hypertension, psychiatric and behavioural disorders, potency disorders, testicle atrophy and gynaecomastia in males and to some degree reduced fertility. Other AEs include masculinisation in women. In 2004, an interactive website was created with a possibility for the misusers to report AEs. We investigated the characteristics of the misusers of AAS, other hormone pharmaceuticals and dietary supplements and their misuse profile.

Objective: To study the pattern of misuse of illicit hormone pharmaceuticals and related compounds in order to develop preventive strategies, and to identify and describe physiological, social and psychiatric AEs in men at onset of adolescence.

Methods: An anonymous self-reporting questionnaire at the Anti Doping Hotline's website was established. It contained questions concerning AE, the misused substances and effects on quality of life. The form was filled in by a total of 48 anonymous male misusers to the Anti Doping Hotline. 27 males aged 20–40 yr with an age at onset 14–19 yr and 21 individuals aged 16–19 yr at the time for self-report were recruited to the study.

Results: Misuse of mixed drugs (AAS and other related hormone pharmaceuticals) was higher in the older age group (41%) than the younger group (9%). Having a positive experience of the abuse, despite AEs, was more common in the younger group (38%), compared to the older group (22%). Almost everybody in both groups had experienced AEs (except for one individual in each group who only reported a positive experience). Clenbuterol, a beta-2 adrenergic agonist, was reported in the older group. A higher rate of misuse of growth hormones was noted among the older subjects (29%). The most common AEs among males in total were psychiatric symptoms such as anxiety, aggressiveness and depression. No difference in AE frequency was found between the two age groups.

Conclusion: Our data verify a different pattern of the abuse of illicit hormone pharmaceuticals and related compounds in young and old males. Among the males with a longer duration of misuse, a mixed use of hormone pharmaceuticals was more common. Having a positive experience of the abuse despite AE was more common among the younger subjects with shorter duration of misuse. However, there were no differences in types of reported AEs.