



NEONATES WORKSHOP

WORKSHOP ON REGULATORY AND SCIENTIFIC ISSUES RELATED TO THE INVESTIGATION OF MEDICINAL PRODUCTS INTENDED FOR NEONATAL USE

MINUTES

This workshop, chaired by Prof. John van den Anker, was hosted at the EMEA on Wednesday 11 October 2006 and intended to provide an in-depth review and scientific discussion on all aspects related to the investigation of medicinal products in the neonate (see Annex 1 for agenda).

Professor van den Anker welcomed participants from Academia, National Agencies, Learned Societies, Industry as well as members of the Paediatric Working Party (PEG), a temporary working party of the Committee for Human Medicinal Products (CHMP) (see Annex 2 for list of participants).

Professor van den Anker introduced the topic by giving an overview of the history of drug development for products used in children, including such devastating events as the sulfonamide related deaths or the grey-baby syndrome caused by chloramphenicol in the 1950's. He addressed the current licensing system and the problem of off-label use of medicinal products in children affecting in particular the neonatal population, where publications have shown that 90 % of infants treated on intensive care units received at least one unlicensed or off-label drug. The current lack of knowledge with respect to medicinal products administered to the neonate is mainly due to the limited population, the difficulties to conduct clinical trials in the neonate, the lack of appropriate infrastructure and ethical concerns. Some achievements have been made in the US through several US Paediatric Initiatives (PREA (2003), Paediatric Research Equity Act and BPCA (2002) Best Pharmaceuticals for Children Act), first introduced by the US government in the 1990's (FDAMA (1997) and Pediatric Rule (1998)) and providing incentives for industry to conduct studies in the paediatric population. Experience already gained through neonatal studies have shown the high variability of pharmacokinetics as well as specific adverse reactions, which can be detected only through studies designed specifically for this age group. He closed his introduction by stressing the objective of this meeting to contribute to the development of a Guideline on Investigation of Medicinal Products in the Neonate by the PEG.

These introductory words set the scene of the workshop focussing on what could be proposed and achieved together, particularly at a time when the new Regulation for paediatric medicinal products will enter into force in early 2007.

Professor van den Anker then addressed issues of organ immaturity when investigating medicinal products in the neonate. Clinical trial protocols for studies conducted in the neonate will have to take into consideration a number of factors, accounting for the fact that neonates represent a special population with substantial differences due to immaturity of organ systems, unique clinical conditions, genetic factors as well as the rapidly ongoing maturation. Simple extensions of adult trials to the neonatal age group cannot be sufficient. Professor van den Anker also stressed the need to obtain pharmacokinetic (PK) data in the neonate, reflecting the rapidly changing systems of adsorption, distribution, metabolism and excretion in the neonate. He stressed that one of the major challenges in paediatric clinical pharmacology is to further describe these highly variable physiological processes. He continued his presentation by describing major physiological pathways known and described already, e.g. developmental changes in gastric pH of the neonate, renal function maturation including the high variability of glomerular filtration rate (GFR), physiological changes in body composition and aspects of ontogeny of drug-metabolizing enzymes and transporters. These complex processes are further highly susceptible to pathophysiological changes due to the clinical condition of the neonate.

By summarising the various factors influencing drug disposition and metabolism in the neonate, Professor van den Anker concluded that there was a clear need for studies in the neonatal population in order to determine pharmacokinetics, ¹pharmacodynamics, the appropriate dose as well as safety and efficacy of medicinal products used in this specific age group.

The following presentation by Professor Joerg Breitreutz addressed aspects of formulations for medicinal products used in the neonate. He highlighted that some of the most severe cases of adverse drug reactions (ADR's) affected children in particular. These were partly caused by the use of improper formulations, containing excipients frequently used but highly toxic for children and even more for neonates. He listed eight main criteria's for child appropriate formulations, including such factors as bioavailability, non-toxic excipients to socio-cultural acceptability. He also addressed the *CHMP Reflection Paper on formulations of choice for the paediatric population*¹ and the recommendations made on age appropriate dosage forms. The rating of rectal enema as the dosage form of choice in preterm newborn infants was challenged by some of the participants, as this seemed to be not in line with current recommendation and expert opinions. Formulations predominantly used in the neonate are parenterals, oral liquids as well as rectal and topical formulations. Professor Breitreutz highlighted the risks of treatment errors when using parenteral administration, e.g. during preparation or administration of the medicinal product. Numerous factors impact on potential medication errors but with regard to neonates specific concerns are related to incompatibility of different substances in the infusion line, osmolarity and the use of inadequate solvents, fluid volume and the risk of over- or underdosing through lag-volume in iv fluid lines. He further addressed excipients, e.g. of benzyl alcohol, propylene glycol as one of the major problem of toxicity in the neonatal period. Propylene glycol may lead to hyperosmolarity while immaturity of the enzyme alcohol dehydrogenase accounts for the toxicity of benzyl alcohol in the early neonatal period. Professor Breitreutz also stressed the risk for neonates through toxic substances adsorbed or penetrating through tube material (PVC, polyurethane) or desorbing from tube and packaging material (diethyl-hexyl phthalate, aluminium etc). However, some potential alternative drug administration routes have been developed recently, although not limited or specific for neonatal use. These include administration through spraying, oral syringes, pacifiers and dropper tubes as well as a number of flavours to increase compliance. Dosing oral liquids e.g. through dosing spoons may create dosing errors, while there is some evidence that the use of dropper tubes is advantageous. In any case, medicinal products developed for neonatal use should be liquid formulations rather than solid. He concluded his talk by stressing that alternative concepts and drug formulations for the neonate need to be developed. During the discussion, the need for a list of age appropriate excipients was expressed although it was acknowledged that this would be a very complex task to undertake.

The next speaker, Prof. Gregory L. Kearns addressed aspects of pharmacokinetics and pharmacodynamics as an expression of ontogeny and pharmacogenetics in the neonate. Following an introductory part addressing the relationship between genetics, environment, disease and ongoing development of the neonate on drug response, Professor Kearns highlighted the principles of drug biotransformation and the changes in metabolic capacity in the first years of life. Many cytochrome P450 isoforms are less active in the foetal and neonatal period but increase in the early weeks of life. Expression and maturation are isoform dependent and may highly vary between individuals. Professor Kearns addressed the ontogeny of the most important CYP isoforms. For instance, CYP 3A7 is the major isoform expressed in the human foetal liver and increasing activity during pregnancy with maximum levels in the first week of postnatal life have been described in in-vitro studies. The influence of nuclear receptors on the expression of drug metabolising enzymes (DME's) and transporters and the variable expression in early life was highlighted. Some "orphan" members of the nuclear receptor superfamily play an important role in the expression of DME's. For instance, HNF α functionally interacts with other nuclear receptors, affecting drug metabolism by regulating CYP3A expression. Professor Kearns described the importance of pharmacogenetic factors by stating the example of CYP2C9 and CYP2C19 with several allelic variants and their impact on pharmacodynamics and kinetics. Another important variable which has to be taken into account when studying medicinal products in the neonates is the potential effect of varying diets on the level of CYP expression and subsequent drug metabolism. Caffeine elimination for instance is decreased in breast-fed children while formulas could activate Ah-

¹ CHMP Reflection Paper on Formulations of Choice for the Paediatric Population
(<http://www.emea.europa.eu/pdfs/human/peg/19481005en.pdf>)

receptors (aryl-hydrocarbon receptors, AHR). The last part of his presentation addressed the potential impact on drug administration in early life on the expression of receptors. Although only few data on receptor maturation are currently available, recent evidence for instance suggests that e.g. administration of SSRI's (selective serotonin re-uptake inhibitors) during pregnancy may influence receptor expression in the newborn.

The next talk by Professor Fellman addressed the issue of pain in neonates. With nociceptive pathways developing as early as the 2nd trimester, pain can be experienced from birth and even before. The neonate, being exposed to multiple, often painful procedures has long been neglected in this respect. It is only in the past 2 decades that pain in neonates and newborns has become a recognised issue, although there is still little consensus among experts on the acceptable degree of invasiveness of certain procedures, the need for pain relief for neonates and preterm infants treated on intensive care units as well as on how to prevent and assess pain in the neonate. There is evidence available that painful procedures might be experienced by the neonate treated in a hospital as often as 14+/- 4 times a day (Simons et al, Arch Pediatr Adolesc Med 2003), while this number seems to be negatively correlated with gestational age. While a number of pain scales for the evaluation of acute (procedural) pain exist, differing assessment for instance between nurses and physicians as well as the use of inappropriate pain scales remain a problem. Prof. Fellman presented new insights in measures to prevent pain in the neonatal period through alternative interventions and non-pharmacological pain relief. Research on behavioural and physiological indicators provides evidence that for instance positioning, facilitated tucking, use of pacifiers as well as sensorial stimulation (sucrose, music) may have pain relieving or preventing effects. Professor Fellman concluded that there is a clear need for more evidence-based medicine in neonatal pain management and prevention as well for appropriate assessment tools for chronic pain in children.

The morning session ended with a panel discussion. It was highlighted that there is evidence available that experience of pain in early lifetime has an effect on pain perception in later life. With numerous pain scales being developed, the need for new objective measures for pain evaluation (PET, infrared spectroscopy) was stressed. With regard to further investigation of pharmacogenetic factors of drug metabolism, it was agreed that routine DNA collection during clinical trials in the neonatal age group without a predefined objective should be avoided.

Professor Pieter Sauer opened the afternoon session with his presentation on ethical aspects of clinical studies in the neonate. As neonates cannot consent to participate in clinical trials themselves, special precautions and considerations have to be taken to protect the neonate. Although according to Prof Sauer, there is no formal legal basis, parents - by supposedly acting in the best interest of their child - will have to consent for their child to take part in the trial. He highlighted the responsibilities of ethical committees and institutional review boards to evaluate whether trials including the neonatal population are necessary and appropriately designed. This, among other aspects includes safeguards to ensure that trials are feasible to provide meaningful results, rights to freely publish results and above all to weigh up the risks and burdens for the neonate involved in the trial. After referring to the legal basis for clinical trials, Prof Sauer concluded that clinical trials in the neonate have to meet the requirement of minimal risk and minimal harm/burden and can only be conducted if the expected data cannot be extrapolated from adult studies and if either the infant itself or the group of infants could benefit from the results. He highlighted that the definition of what is minimal risk and burden for the neonate is however still largely debated among experts. The inclusion of a placebo arm in neonatal clinical trials might be acceptable if necessary to obtain proper answers that cannot be obtained without including a group receiving no treatment. Prof Sauer exemplified the difficulties of ethical considerations of clinical trials by presenting some examples of trials submitted for ethical approval. He concluded that research in children including newborn infants is important but requires careful consideration and unique and special safeguards.

A lively discussion on retrospective consent in emergency trials, consent of parents before birth, financial reimbursement of trial participants and the need for non-therapeutic studies in children followed his presentation.

The following presentation by Prof. Gerard Pons focused on methodology, study design and statistical approaches in neonatal clinical trials. Prof. Pons reemphasised the fact that simple extrapolation from adult data based on a proportionality rule is not appropriate. Due to the various differences in drug

metabolism in the neonatal population, separate studies in the neonate to study efficacy and safety of a medicinal product will often be necessary. This requires measures to reduce and prevent invasive procedures and pain during neonatal studies. According to Prof. Pons, non-invasive measures such as transcutaneous measurements or surrogate markers require careful validation. He stressed the need for sensitive assays and small number of blood samples to be withdrawn during clinical trials due to the small blood volume of the neonate (85ml/kg). If possible, available data on maturational profiles of the neonate should be used to adjust the dose. He highlighted that the knowledge of ontogeny of the processes involved in drug elimination will determine the lower age limit for extrapolation from data in adults or older children. Other measures to avoid unnecessary studies in children include the use of available data, e.g. through population PK or published data and meta-analysis, if possible. New alternative approaches for PK studies, the population approach and the rich-data individual approach, were presented. He also explained the new promising Bayesian sequential analysis for dose-finding studies in neonates. This method, by using a posteriori estimated probabilities of success for tested doses, allows to calculate and adjust the dose after each individual tested, thereby requiring only a limited number of patients. No placebo group is necessary when using this approach. As recruitment and invasiveness are limiting factors for neonatal studies, the need for new endpoints and surrogate markers was highlighted. These endpoints may need to be adapted to the patient's age. This, for instance applies to scales used to assess pain in children. Visual analogue scales for self-evaluation might be used as early as from 4-6 years. A number of validated scales for the assessment of post-operative, acute and chronic pain for younger children are also available. Dr. Pons stressed the need for appropriate post-marketing studies for medicinal products used in children. This has to include but is not limited to long-term prospective follow-up studies to evaluate the influence on growth and maturation, reproductive capacity, cognitive and psychological development as unpredicted side effects and late toxicity on developing organs may occur far beyond the neonatal period. He concluded that although a number of innovative methodologies are being developed, it is not expected that classical approaches will be replaced. Clearly, the limitations of new approaches have to be explored, making neonatal clinical pharmacology a challenging area for methodological research.

Dr. Dirk Mentzer presented pharmacovigilance and safety aspects of neonatal clinical trials. He started by highlighting existing guidelines addressing aspects of clinical trials in the paediatric population including pharmacovigilance in children. New recommendations focusing on clinical trials in the neonate are currently under development in view of the challenges in the future. Underreporting of adverse reactions in the neonatal population according to him is one of the major problems, complicated by multimorbidity and polypharmacy of the neonate treated on intensive care units. Additionally, training of physicians is needed. One of the most important challenges in neonatal pharmacovigilance is the follow-up on long-term effects on growth and maturation including e.g. neurological, behavioural as well as immune maturation. Available knowledge on organ maturation as well as data generated through juvenile animal studies should be considered when assessing any risk management plan or pharmacovigilance plan for the neonatal population. Dr. Mentzer identified 4 main areas of action for neonatal pharmacovigilance: Risk communication through rapid-alert systems, periodic safety update reports and comparable systems as well as the identification of known and potential risks are among these. This could be achieved by establishing more patient registries, signal detection tools as well as to increase research in pharmacovigilance. Additionally, marketing authorisation holders and regulatory authorities have to provide appropriate educational information to increase parents awareness thereby increasing enhanced reporting. The last main aspect to improve pharmacovigilance in the neonatal population covers surveillance and controlled trials, such as post-marketing safety studies or epidemiological studies.

During the discussion following his presentation it appeared that coordination and improvement of the ongoing activities (EudraVigilance) and financing long-term safety studies were among the greatest concerns with regard to pharmacovigilance in children.

Professor van den Anker closed the meeting by thanking the speakers for their excellent presentations and the fruitful discussion from the assembly. He summarised the main conclusion of this workshop:

- The overall objective of the workshop has been achieved by discussing aspects on the investigation of medicinal products in the neonate to contribute to the development of a Guideline for Investigators and Industry.

- Neonatal clinical trials remain challenging for physicians, clinical pharmacologists, regulators and industry due to numerous specifics of this highly vulnerable population.
- In view of the increasing number of neonatal trials, collaboration between experts, regulators and industry is needed.
- Routine DNA collection during neonatal clinical trials should be avoided.
- There is an increased need for age appropriate formulations for the neonatal population.
- A single European ethics committee needs to be established to increase harmonisation and avoid divergent approaches to neonatal clinical trials.
- New measures to avoid or minimise pain and distress in the neonatal population during clinical trials have to be developed.
- New methodological approaches for clinical trials in the neonate exist, but have to be further explored.
- Pharmacovigilance in the neonatal population requires specific tools and considerations to appropriately detect adverse reactions and in particular address long-term safety risks.

Annex 1: Agenda

Annex 2: Introduction and presentation Prof. van den Anker

Annex 3: Presentation Prof. Breitkreutz

Annex 4: Presentation Prof. Kearns

Annex 5: Presentation Prof. Sauer

Annex 6: Presentation Prof. Pons

Annex 7 : Presentation Dr. Mentzer