European Medicines Agency

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WORKSHOP ON MEDICINES FOR THE TREATMENT OF PAIN IN CHILDREN

This workshop co-chaired by Dr Kevin Connolly, Dr Daniel Brasseur, Dr Chantal Wood, and Dr Agnès Saint Raymond took place at the EMEA on Thursday 28 October 2004 (Annex 1).

Dr. Connolly welcomed all participants, from Academia, National Agencies, Industry, Patients' organisations as well as members of the Committee for Human Medicinal Products (CHMP) and its Paediatric Expert Group (PEG) (Annex 2). Dr Connolly acknowledged the importance of this meeting, particularly in view of the future Regulation on paediatric medicines. Treatment of pain represents a good paradigm of the needs with respect to children's medicines, all the more so as all children, including the smallest neonates, experience pain.

As an introduction, Dr. Brasseur outlined that opinions and attitudes about treatment of pain in children have changed drastically in the last two decades. However, under-treatment still remains common practice particularly in newborns and for chronic diseases. The reasons for such an unfortunate situation pertain to a lack of clinical information and appropriate products, as well as different cultural approaches. These introductory words set the scene of the workshop focussing on what could be proposed and achieved together, particularly at a time when a new Regulation for paediatric medicinal products is open for public debate (Annex 3).

The first speaker, Dr. Howard, Consultant in Paediatric Anaesthesia and Pain Management at Great Ormond Street Hospital for Children (GOSH), London, England, presented the current state of management of pain in children (Annex 4). Pain is still underestimated in children and current research evidence has clearly demonstrated that children of all ages, even the most immature pre-term infants are capable of experiencing pain. He distinguished three situations: acute pain, chronic pain and pain in neonates. For acute pain, the problems relate mostly to the fact that available treatments are not being used and that new treatments are slow to be developed. For chronic pain, where pain aetiology may be different to that in adults, there is very little information about the efficacy of the treatments used, which in most cases are not licensed for use in children. Pain in neonates is a more complex area, as there are changes in pain processing mechanisms during the postnatal development as well as pharmacodynamic/pharmacokinetic changes. The toxicity and long-term consequences of therapy are important aspects to be considered. In addition, early experience of pain may produce long-standing changes in pain perception. Dr Howard concluded by listing what he believed should be done to improve pain management in children i.e further investigation of mechanisms and developmental changes, better designed clinical studies, permanent evaluation of evidence, education and training, and accelerated transition of science into trials and clinical practice.

The next speaker, Dr. Brion, Professor of Clinical Pharmacy at Paris V University and Chief Pharmacist at Robert Debré Hospital, France, addressed the problem of paediatric formulations for pain control (Annex 5). After summarising the different compounds detailed in the WHO three-step ladder for the treatment of pain, she reviewed the different pharmaceutical forms. Oral forms approved only for adult use but often used in practice for children, lead to a high risk of administration errors and problems (cutting, crushing, sieving, imprecise dose). The classical forms used in paediatrics (effervescent tablets, powders or granules packets, liquid forms) have their advantages and drawbacks; rectal forms have debatable interest because of administration and bioavailability issues; parenteral dose forms authorised for paediatric use are often available in inappropriate concentrations and volumes leading to a high risk of administration error and potential overdose (typical ten-fold error). Although the market is often described as small, it seems from the presentation that there is a wide range of formulations available. According to her, the following pharmaceutical forms are the most convenient for use in children: oral solutions and newer forms like orodispersibles, and non-invasive forms such as patches (matrix-type system). If the form requires a measuring device, this should be very precise (pipette/syringe rather than spoon). To avoid any risk of confusion, it was suggested that the name of the product be also mentioned on the device. Multidose formulations should be preservative-free. She also highlighted that the way the dosage is expressed on the packaging is often confusing (e.g. mg/ml, mg/l, mg/ampoule or even %) increasing the risk of medication errors especially in an emergency setting. Such errors may occur as well due to similar design/colours in packaging. Participants were reminded that currently there is not only a lack of products indicated for the treatment of children, but also a lack of suitable formulations. Within the current legislative framework, there is no legal tool to oblige a company to develop a formulation convenient for use in children. Finally, the problem of differences in availability of suitable formulations across the various EU Member States was evoked.

The next talk by Dr. Franck, Professor and Chair of children's nursing research at the Institute of Child Health, University College London and Great Ormond Street Hospital for Children NHS Trust, focused on how to assess pain in newborn babies (Annex 6). Although over the last 25 years, there has been research measurement of pain in infants and various scales developed, there is not yet consensus on the optimal measures. She reviewed the research on behavioural and physiological indicators of pain and the challenges in distinguishing pain-related signs from simultaneous distress. She illustrated her talk with an example on procedural pain and stress during the early post-operative period. She concluded on the implications for research on pain medicines, highlighted the need for defining endpoints for pain assessment in children, (in improving their sensitivity and specificity), for differentiating between analgesia and sedative effects, and for developing measures of important side effects.

Prof. Fellman, Professor in Neonatology, Lund University, Sweden and University of Helsinki, Finland, presented the challenges in pain management in neonates (Annex 7). Controversies still exist concerning the severity of pain and need for pain relief for preterm infants undergoing intensive care. She reviewed the clinical practices in 3 painful situations: intubation, postoperative pain and mechanical ventilation. She presented the results of a published trial on the efficacy and safety of morphine versus fentanyl in neonates requiring mechanical ventilation, as well as that of a published study on morphine versus placebo. She concluded by recommending individualised care to prevent pain (with routine, repetitive pain assessment, low doses of opioid infusion with boluses, non-steroidal anti-inflammatory drugs). If pharmacological treatment is required, the gestational and postnatal ages should be considered, as well as the disease and possibly pharmacogenetics. It was reiterated that pain in neonates does exist; analgesics can be effective, but there is a need to rationalise their use. There is a need for well-designed and well-executed trials on premedication for intubation and on optimal pain relief during intensive care in neonates.

The morning session ended with a panel discussion summarising the main points. All participants agreed that children suffer from pain and that we are not doing enough to prevent/alleviate it.

There is however a need for education of healthcare professionals to overcome under-treatment and differences in attitudes and practices towards pain management in Europe, especially in neonates. There is a clear need for more meaningful research through good quality cooperative/international studies, especially in neonates. There is a need for an extrapolation of the pain measurements from research to clinical practice. There is a need to rationalise/harmonise products, and for formulations convenient for use in children.

Dr. Hamunen, anaesthesiologist in the Department of Anaesthesia and Intensive Care Medicine, Meilahti Hospital, Helsinki Finland, opened the afternoon session with a presentation on clinical trials in paediatric pain treatment (Annex 8). She briefly highlighted the importance of age in paediatric trials and some general methodology aspects on the design of such studies. There are relatively less therapeutic trials for chronic than for acute pain. She presented the results from two systematic reviews of acute pain treatment to illustrate the problems of trial methodology in the paediatric population. She concluded that for future trials more standardised methodology, including clinically significant outcomes, is needed for both acute and chronic pain. Due to possible ethical issues, the use of placebo in paediatric patients has to be carefully considered. Studies on chronic pain states and data on long-term effects of analgesics on developing CNS are also needed.

Dr Saint-Raymond, Head of Sector Scientific Advice and Orphan Drugs, EMEA, gave an overview of the European Regulatory framework and of the proposed future Regulation on medicines for children (Annexes 9, 10 and 11). She then presented the Paediatric Expert Group of the CHMP and its activities. In particular, she explained the initiative taken by the PEG to identify the paediatric needs in the different therapeutic areas. One of the areas studied was pain and the preliminary results of this assessment have triggered this Workshop. She acknowledged the limitation of the methodology used. The next step will be the publication of the list of products for which data are needed.

The final presentation from Dr. Wood, Responsible of the Pain Treatment Unit, Robert Debré Hospital, Paris France, highlighted the differences in practice of pain management in Europe (Annex 12). She illustrated her talk with examples showing the situation of paediatric palliative care for some EU Member States, including the new ones, in particular with respect to the consumption of opioids. This again supported the evidence that children are still under-treated.

The discussion that followed focused mainly on the differences in clinical practices across Europe. It was agreed that the practices should be based on scientifically sound data. Although the Agency has no remit in harmonising the medical practice, getting better information on efficacy and safety of medicinal products would ultimately favour better practices. Patients' representatives emphasised also the role of education. In this context, there should be efforts to increase awareness of the problem of pain in children, and the importance of its management should be promoted. Another important aspect raised was that studies should take into consideration the influence of pain on psychological and social dimensions. To obtain conclusive results, cooperative trials should be encouraged and more cooperation between Member States is warranted. From their part, patients' organisations should promote the importance of and need for taking part in clinical trials.

Finally, the conclusions of the day were positive, insisting on potential collaboration between the different partners to tackle the challenges at each level:

- Efforts should be made by Industry and Regulators to reduce existing differences between Member States relating to availability of pain medicines in children, in terms of formulations, posology, or indications. This should ensure proper access of children of all ages to existing pain treatments.
- Where medical needs are clear, Industry should develop appropriate formulations and provide further studies and data on long-term use to allow proper prescription of pain medicines in children including neonates. This may be best achieved in collaboration with Academia.
- Regulators should develop adequate guidance documents to help the development of medicines for pain in children. For example, there is a need for standardised methodology in measuring pain in the youngest, and for data requirements on long-term treatment.
- There is a need to harmonise pain management in Europe through specialists and academia, and to further educate all concerned physicians in recognising and treating pain.
- Patients' organisations have a shared responsibility and should raise the awareness of parents on the benefit for all children, including theirs, obtained through children's participation in clinical trials of pain treatments.

The Chairpersons closed the meeting thanking all the participants for the fruitful and active discussion.

Annex 1: Agenda
Annex 2: List of Participants
Annex 3: Presentation Dr. Brasseur
Annex 4: Presentation Dr. Howard
Annex 5: Presentation Dr. Brion
Annex 6: Presentation Dr. Franck
Annex 7: Presentation Prof. Fellman

Annex 8: Presentation Dr. Hamunen
Annex 9: Presentation Dr. Saint-Raymond
Annex 10: EMEA/PEG procedure for identifying paediatric needs
Annex 11: Assessment of the paediatric needs for pain
Annex 12: Presentation Dr. Wood