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Human Medicines Development and Evaluation

Conclusions of the Paediatric Epilepsy Experts Group Meeting, held in London 1 September 2009

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1. Aim

A Paediatric Epilepsy Expert Group Meeting was held at the EMEA in London to identify the best possible development approaches for new medicines in the field of epilepsy in childhood and adolescence for the evaluation of Paediatric Investigation Plans.

2. Introduction

The aim of this meeting, i.e. the identification of the best possible **development approaches** for new medicines in the field of epilepsy in childhood and adolescence for Paediatric Investigation Plans was emphasized and an outline of the current situation given. This situation is characterized by the frequency of the condition of 'epilepsy', the potential severity, the poorly defined aetiology and pathophysiology, the insufficient definition of the drug target and mechanism of action and the poorly met needs especially for refractory epilepsies with patients being rarely seizure free.

3. Conditions and priorities

The experts agreed that epilepsy and epileptic syndromes in neonates should be prioritised (see section 6.). There is also a specific need for studies in patients from 1 month to less than of 2 years of age (apart from infantile spasms or idiopathic generalized epilepsy). There is a high incidence of off-label use and treatment mainly based on individual experience.

Suboptimally designed controlled studies may still be unable to inform clinical practice, e.g. standard placebo-controlled approaches to study Lennox-Gastaut syndrome were judged as being rather unhelpful, as children included in these trials were generally too advanced in their disease to truly benefit, and seizure reductions observed were generally unsustained beyond the typically studied period of three months.

The question whether certain modes of action of anti-epileptic drugs (AED) could predict limited or exclusive use in children is difficult to answer, as in many cases the mode of action is not known exactly.

4. Non-clinical studies

There is a need for juvenile pre-clinical studies in comparison to pre-clinical studies in adult animals as well as well defined neurotoxicity studies and long term follow up in rodent models for the development of AEDs for all children, but in particular for patients below the age of 4 years (see 6.2).

The use of appropriate models for neurodevelopment was underlined, but it also has to be taken into account that animals have a large hippocampus and therefore results with these models are more specific for temporal lobe epilepsy. However there are also other models which are preferably used in academic research settings, however, there is still the need for further development of animal models for child epilepsy and neurotoxicity. There must be caution in exploring activity in animal models which might not reflect efficacy in humans, but might be more appropriate for investigating safety.

5. Clinical studies

5.1. Pharmacokinetics

The study of influence of age and maturation on the pharmacokinetics is of special importance. The invasiveness should be limited e.g. by drawing small blood samples, using population approaches on sparse samples and minimising the number of samples and the number of patients recruited. The reliability and the precision of the estimates however, should not be compromised.

5.2. Study design

An overview of methodologies for small numbers of samples (modelling, simulation, extrapolation) and for small number of patients was presented. For the latter the issue of homogenous populations, enrichment with withdrawal and sequential designs were discussed.

It was stressed that studies have to be designed according to the characteristics of the specific epilepsy syndrome and the knowledge about the product with respect to the duration of the trials, specific endpoints, development of biomarkers and receptor studies, small population designs and analyses.

5.2.1. Observational studies

There was agreement that the paediatric epileptic syndromes with a low incidence need a different approach. One possibility would be to conduct observational studies including different epilepsy syndromes followed by randomised controlled trials for each indication in those patients where a positive, clearly defined signal was detected. The syndromes to prioritise and to include in observational trials have to be defined in the inclusion criteria. As a first step only patients with a definitive diagnosis should be included. It was reminded that these studies can not be seen as a basis for an authorisation.

5.2.2. Inclusion criteria

There were several proposals to include patients ideally at an early stage of the epilepsy, even before the definitive diagnosis can be made. It is not proven whether stopping or reducing seizure frequency also can stop the course of the disease, for this an early intervention might be needed. Stratification according to diagnosis could follow later. This would also reflect clinical practice which is getting more aggressive. The definition of refractory epilepsy in children, i.e. the failure of 2 appropriate AEDs and no seizure freedom for at least 2 months could be varied according to condition, e.g. in infantile spasms inclusion into trials could be done after unsuccessfully trying 2 AEDs in the time frame of 10-14 days, whereas for Rolandic epilepsy this decision could be made if seizure freedom cannot be reached for at least one year.

5.2.3. Control

Placebo design is acceptable in an add-on design, however for monotherapy studies it would also be acceptable, as long as adequate escape mechanisms with an appropriate rescue medication are defined.

For active control it was remarked that often the state of knowledge is not sufficient for the first generation AEDs, therefore the usefulness of an active control was questioned under such circumstances particularly without any placebo control.

5.2.4. Withdrawal design

Withdrawal data do not show results of treatment initiation but rather of withdrawing it. Therefore these data can be only regarded as supportive.

5.2.5. Extrapolation

Extrapolation has to be differentiated in extrapolation for disease and for drugs. Juvenile animal studies as well as PK and safety studies are needed in general as early as possible.

There was general agreement that results of studies for partial onset seizures in adults could be extrapolated down to the age of about 4 years.

5.2.6. Long-term Safety and Efficacy

Regarding long term studies without control it has to be kept in mind that the background should be defined well. The need for studying long term cognitive effects including neurodevelopment, learning as well as growth, sexual maturation and endocrine functions (see 6.4.) was underlined.

The duration of the long-term studies should be at least one year, depending on the type of epilepsy or epileptic syndrome and the age of the patients, i.e. it should be longer the younger the included patients are.

5.2.7. Cognitive testing

For cognitive testing effects of the condition and the drug have to be separated and the background has to be specified, especially if there are no controls. However the need for assessing cognitive function was underlined especially also for encephalopathies. Sharing of experience and appropriate validated test methods for different age groups should be encouraged between the experts. Age milestones to be included for cognitive testing were 2-2.5 years, 4 and 6 years.

6. Studies in neonates

The situation in the neonatal age group particularly differs from the other paediatric age groups and there is not much experience in studying this age subset. In neonates seizures mainly occur with and after infections, strokes, perventricular leucomalacia (PVL), intracerebral haemorrhage, metabolic diseases, malformations and after cardiac surgery.

It was agreed that seizures associated with the conditions ‘hypoxic ischaemic encephalopathy (HIE)’ and ‘stroke’ should be prioritised for studies in neonates.

6.1. Quality

In general intravenous formulations are needed for this age group, however an oral age-appropriate formulation is needed for patients who can be fed orally and for maintenance therapy. It was stressed that a development of an oral formulation for this age-group might be useful, even if the development of an intravenous formulation is not feasible for a specific medicinal product.

6.2. Non-clinical

It was agreed that neurotoxicity studies with a neurodevelopmental follow-up of at least 3 months in rodents is needed. (See also 4.)

6.3. Clinical studies

Pharmacokinetic studies are needed taking into account the points discussed above. Endpoints may not include only seizure count, but potentially also effects on the encephalopathic process (regarding for example long term neuroprotective outcome (increased survival without neurodisability), cognition, communication, EEG). The evaluation should not rely on observation but on EEG (48 hour VideoEEG). Validated scales should be used for assessment of quality of life, well being of the child, neurodevelopment, cognition and behaviour. In certain conditions the use of imaging techniques such as MRI might be needed for diagnosis and assessment of outcome.

Preterm and term infants should be studied separately, possibly in an age-staggered approach starting with the older age group first.

For the duration of short term safety and efficacy trials a time frame of 2-3 weeks was discussed, long term follow-up studies should be specifically designed according to the condition investigated.

7. Further points to be discussed at follow-up meeting

7.1. Approach for monotherapy indication.

7.2. Study design: What is the optimal duration for efficacy studies? Are there age-specific outcome measures? Which safety parameters should be assessed at which time points for the different age groups?

7.3. Further exploration of the situation for the age group of infants.

8. Post-meeting notice

The results of the meeting do not necessarily reflect the opinion of the PDCO. However they were taken into account by the PDCO for commenting on the draft of the CHMP guideline on clinical investigation of medicinal products on the treatment of epileptic disorders.

9. List of participants

Experts Group:

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