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Antiepileptic Drug Development in Children

Considerations for a Revisited Strategy

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Abstract

The European Commission and the European Parliament have acknowledged the specific need for a proper evaluation of new drugs in children. The evaluation of the antiepileptic drugs (AEDs) available on the market illustrates the deficit in therapeutic trials for childhood epilepsy syndromes. Currently, the development of AEDs is mainly performed in children with focal epilepsy, whereas infants and the specific age-related epilepsy syndromes, particularly epileptic encephalopathies, are neglected. Infantile epilepsies remain 'therapeutic orphans', although they are the most frequent and deleterious disorders in the area of epilepsy. In order to circumvent the difficulties faced when conducting AED trials in children, we addressed the question of improving feasibility without decreasing quality, while optimally taking into account paediatric ethical requirements.

For this review, we first raise the issues of paediatric epilepsies that require special considerations for randomized controlled trials (RCTs) in children. Then, we attempt to determine to what extent adult data could be extrapolated to children. Finally, we review innovative approaches that could be used in the evaluation of AEDs in children.

The main specificities of paediatric epilepsies (heterogeneity, severity, cognitive impact, pharmacoresistance, syndrome-specific efficacy profile) are related to brain development and should be taken into consideration when establishing specific guidelines for the evaluation of AEDs in children. Extrapolating efficacy data from adults to children may be possible in focal epilepsy except in infants who need age-specific trials. Epileptic encephalopathies do not exist in adults and require specific trials. Pharmacokinetic data are required below a lower age limit for extrapolation of adult data to be determined in a case-to-case approach. Safety data are required at any paediatric age. RCTs in small but homogeneous populations in each paediatric-specific epileptic syndrome, the use of sequential or responder-enrichment designs, and population pharmacokinetics represent potentially promising approaches to evaluate drugs in children in an efficient way.

Drug labelling frequently includes disclaimers mentioning that safety and efficacy have not been established in children. This is particularly true for neonates (birth to 28 days) and infants (29 days to 2 years). As a consequence, paediatric practice involves the use of 'unlicensed' or 'off-label' medicines from adults or older children. The percentage of such prescriptions for children reaches two-thirds in hospital settings, 90% in intensive care units and about one-third in office-based practice.[1]

Developing drugs specifically for children is particularly important because paediatric diseases are different from those of adults in terms of aetiology, mechanisms, clinical or biological features, and course. Some diseases only occur in children. Children are different from adults with respect to pharmacokinetics and pharmacodynamics that change according to age. Some adverse events only occur in children who undergo growth and maturation. However, performing randomized controlled trials (RCTs) in children may raise specific technical (biological sampling, assessment of drug effect), logistic (recruitment) and financial (cost considered to be high for a small market) as well as legal (informed consent) difficulties. To minimize these issues, financial incentives have been promoted within the last decade in the US and the EU in order to encourage pharmaceutical companies to perform trials specifically in children. A regulation on medicinal products for paediatric use was in December 2006 by the European Parliament.[2]

However, the paediatric population remains a therapeutic orphan.[3] The following ethical dilemma is to be faced in children: they should be protected from the potential risks of research but they may be harmed when given inadequately studied medicines. Therefore, on one hand, unnecessary studies should be avoided and the number of patients exposed to drugs under investigation should be limited. On the other hand, children have to benefit from research and the necessary data have to be collected. In order to fill in the deficit in paediatric studies, while meeting the ethical requirements, a first approach consists of determining whether some results of trials conducted in adult patients could be extrapolated to the paediatric population. A second consists of using or developing for children innovative strategies that limit the number of patients involved.

Epilepsy is an excellent opportunity to reconsider the drug development strategy in children. Epilepsy is the most frequent serious neurological disease in children. It may adversely affect brain function to such an extent that the notion of epileptic encephalopathy has been coined, where motor or cognitive functions are altered as a consequence of epilepsy itself.[4] Epileptic encephalopathies represent about one-half of the pharmacoresistant epilepsies in the paediatric age range, the other half being epilepsy with focal onset seizures (focal epilepsy). Epileptic encephalopathies are age-related, the best identified syndromes are West syndrome (infantile spasms), Dravet syndrome, Lennox-Gastaut syndrome, epileptic encephalopathy with continuous spike waves during sleep (CSWS), Landau-Kleffner syndrome and Rasmussen encephalitis. There is growing evidence that appropriate treatment may improve brain function, provided it is given early enough, even when epilepsy is symptomatic of brain damage.[5,6] However, the resistance of epilepsy to presently available medications in most of these patients is a major concern,[4] and these children therefore require new therapeutic compounds.

The first paediatric RCTs with antiepileptic drugs (AEDs) were performed in the 1990s. Since then, very few have been performed in children compared with adult patients. There is a maximum of a single efficacy trial for a given drug in children, whereas in adults most trials are replicated. No RCT was completed in children before the drug had been approved for adults and therefore available on the market, making paediatric recruitment still more difficult. Since the regulatory guidelines only require studies in indications already granted for adults,[7] most RCTs in children involve focal epilepsy,[8-12] although none of them include patients aged <2 years. Very few studies involve epileptic encephalopathies, such as Lennox-Gastaut syndrome,[13-15] Dravet syndrome[16] or West syndrome.[3,17,18] Needs are particularly crucial in infancy because this age

range has the highest incidence of epilepsy, and the highest risk of cognitive dysfunctions and severe pharmacoresistance.[19,20] In the past 15 years, only one compound, vigabatrin, has been approved for children <2 years of age compared with more than ten for adults. Unfortunately, this agent produced retinal toxicity. Recently, RCTs were initiated with oxcarbazepine and levetiracetam in infants having partial onset seizures and some pharmacokinetic studies were performed in young children.[21] Although these efforts to develop AEDs in infantile epilepsy are encouraging, major needs are still ignored, namely those regarding epileptic encephalopathies.

The strategy to develop new AEDs specifically for children needs to take into account some challenging specificities: (i) childhood epilepsy is very heterogeneous, it includes many different syndromes each exhibiting a different course, each one being a rare disease;[22] (ii) in epileptic encephalopathies deterioration may occur within a few weeks as a result of very active epilepsy and soon become irreversible; and (iii) there is a 'syndrome-specific efficacy profile of drugs'[23] and good evidence that some AEDs may specifically worsen some of these syndromes.[4]

This review first raises the issues of paediatric epilepsies that require special considerations for RCTs in children. Then, it attempts to determine to what extent extrapolation from adult data would be possible in a pragmatic way. Finally, it describes possible trial designs that could take these issues in account and improve the strategy of development for new AEDs in children.

1. The Specificities of Epilepsy in Children and Implications for Clinical Trials

The main characteristics of paediatric epilepsies are high-seizure frequency or severity and/or major interictal paroxysmal anomalies, risk of cognitive deterioration and a possible switch from one syndrome to another with increasing age. In addition, pharmacoresistance develops early, thus early treatment is a condition of efficacy. All these characteristics are linked to brain development and maturation.

Neuronal excitability is diffusely increased in the immature brain because of a number of factors, including increased number of synapses, transient expression of excitatory receptor subunits and the fact that GABA is excitatory during early postnatal life.[24] The risk of epilepsy is therefore increased in early life: epilepsies are more frequent, more active with a high-seizure frequency and/or major interictal paroxysmal anomalies compared with that of adults. Developmental hyper-excitability also interferes with the progressive organisation of neuronal networks that sustain cognitive development: epileptic discharges take place in the same networks and may thus compete with cognitive development. These particularities are all illustrated by epileptic encephalopathies that are age-dependent conditions. The cause of cognitive deterioration is either repeated severe seizures (e.g. Dravet syndrome) or diffuse and continuous activity of spikes and slow waves (e.g. West syndrome and epileptic encephalopathy with CSWS). Developmental hyperexcitability progressively decreases during childhood, with a time-course depending on location within the brain.[25,26] Epileptic encephalopathies may therefore disappear spontaneously after a few months or years, although the patient is often left with severe cognitive sequelae. Others may switch from one syndrome to another, from birth to adolescence (e.g. Ohtahara syndrome, infantile spasms and Lennox-Gastaut syndrome), or switch from focal epilepsy into generalized seizure disorder and vice-versa, either in infancy (infantile spasms) or in childhood (CSWS, Lennox-Gastaut syndrome).

One consequence of this possible sequence is that a previously useful AED may become dangerous (e.g. carbamazepine[4]). Another consequence is that different AEDs may sequentially become the best choice for successive epilepsy syndromes, such as vigabatrin for infantile spasms[27] and then lamotrigine for Lennox-Gastaut syndrome,[15] a frequent sequence in children with tuberous sclerosis.[28]

Regarding pharmacoresistance, one predictive factor is the onset of epilepsy <1 year of age.[19,20]

The persistence of some features of the immature brain and the persistence of seizures maintain brain hyperexcitability.[29] Therefore, in this more than in any other age group, 'seizures beget seizures'.[30] Instead of producing lesions as they do in the adults, seizures in an immature brain cause reorganisation of neuronal networks,[24] altering cognitive development and organising pharmacoresistance, although no damage is visible on structural imaging. Unlike in adults, early treatment seems to prevent seizure refractoriness in some instances in young children,[5] in addition to improving cognitive functions.[6]

As a result, the AED trial guidelines developed for adults cannot be simply applied to children, but should take into account the following specificities of epilepsies in this age range and the ethical correlates.

- Study the efficacy of a given compound in a given epilepsy syndrome: a limited sample of patients may be sufficient to demonstrate the efficacy, provided the group is homogeneous.
- Quantify not only the decrease in seizure frequency but also their potential increase since the spectrum of effects for a given compound ranges from improvement to worsening depending on the epilepsy syndromes.
- Reduce the duration of the evaluation period in double-blind conditions, given the high rate of seizures and the risk of cognitive decline.
- Require total disappearance of seizures as an endpoint as it is a necessary condition for cognitive recovery (not only a decrease of seizure rate by >50%, which is how responders are usually defined in trials for adults). Consider the interictal EEG activity as a surrogate since it is a marker of ongoing epilepsy, and contributes to pharmacoresistance and cognitive deterioration.
- Consider cognitive evaluation as efficacy criteria in addition to the clinical markers of epileptic activity.
- Perform long-term open follow-up studies in order to identify possible tolerance.

Faced with such constraints and in order to fill in the deficit in paediatric AED trials, a first, pragmatic, approach consists of determining whether some results of trials conducted in adult patients could be extrapolated to the paediatric population.

2. Is Any Extrapolation from Adult Trials to Children Possible?

According to the International Conference of Harmonisation E11, "when a medicinal product is to be used in the paediatric population for the same indication(s) as in adults, the disease is similar in adults and children, and the outcome of therapy is likely to be comparable, therefore extrapolation from adult efficacy data may be appropriate".[31] Only focal epilepsies and Lennox-Gastaut syndrome, which often persist into adulthood, could correspond to this situation. Therefore, we tried to compare the findings of RCTs in adults and children in both conditions.

For Lennox-Gastaut syndrome, the comparison proved to be impossible since the three trials reported, conducted with felbamate, lamotrigine and topiramate, respectively, included both adults and children and the study designs and statistical analyses did not take into account the paediatric subgroups.[13-15] In contrast, the RCTs were performed separately in adults and children for epilepsy with partial-onset seizures using five new AEDs: lamotrigine;[8] topiramate;[10] gabapentin;[9] oxcarbazepine;[11] and levetiracetam.[12] A strict comparison of the results in both age groups for each compound was impossible because no plasma concentrations were provided. Nevertheless, studies in both adults and children had the same design and duration, and the dose-ranging design allowed a large range of dosages. Since for any given AED, several controlled trials were performed in adults, we selected the trial with the largest population to compare with the studies in children.[32-36] Considering the most usual and sensitive primary endpoint for efficacy (the percentage of decrease in seizure rate), there was no discrepancy between results in children and adults (table I).

A new compound still under development, rufinamide, recently showed similar efficacy in adults and children with Lennox-Gastaut syndrome, but not in focal epilepsies, although the efficacy rate

Table I. Placebo-controlled add-on antiepileptic drug (AED) trials in children and adults: comparative efficacy

AED	Trial[a] (ages for paediatric trials)	Number of patients	Daily dose	Percentage of seizure decrease vs baseline (%)
Lamotrigine	Duchowny et al.[8] 1999 (2–16 y)	199	150–750 mg	Lamotrigine 36 Placebo 7 p = 0.008 vs placebo
	Matsuo et al.[32] 1993	191	500 mg	Lamotrigine 36 Placebo 8 p = 0.007 vs placebo
Topiramate	Elterman et al.[10] 1999 (2–16 y)	86	6 mg/kg/d	Topiramate 33 Placebo 10.5 p = 0.034 vs placebo
	Faught et al.[33] 1996	181	200 mg 400 mg 600 mg	30%, p = 0.05 48%, p = 0.007 45%, p < 0.001 Placebo 13
Gabapentin	Appleton et al.[9] 1999 (3–12 y)	247	23–35 mg/kg/d	Gabapentin 17 Placebo 6.5 p = 0.04 vs placebo
	US study 1993 (see within Marson et al.[34] 2000)	288	1200 mg 1800 mg	18, significant 30, significant Placebo 8
Oxcarbazepine	Glauser et al.[11] 2000 (3–17 y)	267	30–46 mg/kg/d	Oxcarbazepine 35 Placebo 9 p = 0.0001 vs placebo
	Barcs et al.[35] 2000	694	600 mg 1200 mg 2400 mg	26%, p < 0.0001 40%, p < 0.0001 50%, p < 0.0001 Placebo 8
Levetiracetam	Glauser et al.[12] 2006 (4–16 y)	198	Up to 60 mg/kg/d	Levetiracetam 43 Placebo 16 p = 0.0002 vs placebo
	Cereghino et al.[36] 2000	268	1000 mg 3000 mg	Levetiracetam 33 Levetiracetam 40 Placebo 11 p < 0.001 vs placebo

a For adult trials, the trial with the highest number of patients was selected for comparison.

was close for adults and children.[37] Open-extension trials, also showed quite similar results for sustained efficacy as adjunctive therapy in children and adults.[8,11,38,39] For focal epilepsy, it therefore seems reasonable to extrapolate efficacy data from adults to children aged 2 years and above.

The same does not apply to safety and pharmacokinetic profiles that have to be established in the whole studied paediatric age range. Safety and pharmacokinetic profiles are not specific to the epilepsy syndrome so that data could be drawn from trials in other types of epilepsy than focal. Considering safety, a lot was learned from studies performed in adults, which, to date, have identified the same tolerability profile as in children;[8-12,32-36] adverse events may differ quantitatively (e.g. oxcarbazepine-induced hyponatraemia and topiramate-induced kidney stones being less frequent in children than in adults) but not qualitatively, and no major adverse effect has occurred only in children. Regarding pharmacokinetic parameters, trials disclose similarities between adults and children aged 2–4 years, although the AED dose had to be increased, e.g. by 30% for children aged up to 5 years for gabapentin and lamotrigine,[40,41] by 38% for oxcarbazepine,[42] and by 50% for children aged from 4 to 17 years for topiramate.[43]

Other pharmacoresistant epilepsies occurring at any age in the paediatric population have no equivalent in adulthood. Therefore, no extrapolation from data collected in adults is possible, particularly for epileptic encephalopathies. Given the generally poor response of many of these epileptic encephalopathies to conventional AEDs, one promising innovative strategy would be to develop different types of drugs as therapeutic alternatives. This could include anti-inflammatory or immuno-modulatory drugs, such as corticosteroids or immunoglobulins, proposed in Rasmussen encephalitis, in children and adults, respectively.[44,45] Whatever the therapeutic option selected, the principle of a RCT is an absolute requisite for the drug to be approved in a given indication, in children as in adults. In such rare diseases, innovative methodological approaches that aim to address small sample size without decreasing the power and the quality of the trial are particularly appropriate. They also provide an ethical advantage by exposing the smallest number of children possible to the risk of either administering a potentially toxic compound whose effectiveness is not demonstrated or to withhold the administration of an effective compound for patients assigned to placebo.

3. Innovative Methodological Approaches

Clinical trials in small populations are encouraged by new CHMP (Committee for Medicinal Products for Human Use) guidelines[46] European Regulation. Medicinal products need to be evaluated within a reasonable time, at a reasonable cost and taking into account paediatric ethical constraints. Invasiveness needs to be restricted, and the clinical pharmacokinetics require new methods and approaches.

The population approach is increasingly being used.[47,48] It only requires a few datapoints per patient in a large number of patients; therefore, it applies particularly to the paediatric population because it can cope with sparse data. This limits considerably the number of blood samples required for each patient, thus restricting the invasiveness (pain, blood loss) of pharmacokinetic studies, and reducing time and cost of studies. In addition, it is possible to assess the influence of maturation on pharmacokinetic and pharmacokinetic/pharmacodynamic parameters, having age as a continuous variable instead of using age classes, provided the recruitment is evenly distributed within the whole relevant age range. Dose administration recommendations may subsequently be derived from the calculations in each relevant age class.

Several means allow for the reduction of the number of children required for a RCT without decreasing its statistical power. Including an homogeneous sub-population with a single epilepsy syndrome or aetiology is expected to decrease the inter-individual variability, and to facilitate the demonstration of an expected clinically significant treatment effect size. Using such a procedure, a sample of 41 children was sufficient to demonstrate the efficacy of stiripentol in Dravet syndrome[16] and the randomization of 22 patients proved to be enough to demonstrate the superiority of vigabatrin over corticosteroids in infantile spasms due to tuberous sclerosis.[27] In contrast, trials conducted with lamotrigine and topiramate in Lennox-Gastaut syndrome, pooling various aetiologies, required 90 and 169 patients, respectively, to reach a conclusion.[13,15] The more heterogeneous the population is, the larger the sample size required to detect a significant difference.

The so-called 'enrichment' design consists of selecting responders to the test compound in an open phase and randomizing to either the tested compound or the placebo in the responder-enriched subgroup. The first enrichment trial was conducted in adult patients for add-on tiagabine therapy;[49] the procedure was then applied to study the efficacy of vigabatrin,[50] lamotrigine and stiripentol.[51] However, enriched designs raise ethical issues since the efficacy of a drug can only be demonstrated by temporarily depriving patients of the benefit they had already derived from the drug. A possible withdrawal effect occurring when patients are switched from the active compound at randomization to the placebo group is the key risk and has to be carefully considered using precise and strict escape criteria,

adapted to the studied population and clearly defined in the protocol. Sequential methods are also useful in 'low-resource' conditions because they allow restriction of the sample size. They allow a trial to be stopped as soon as a difference or a lack of difference between arms has been reached (figure 1). In the trial conducted with stiripentol in Dravet syndrome,[16] the triangular test method (figure 1) would have allowed the detection of a benefit with stiripentol from the 25th patient included, which means 1 year earlier than was indeed the case with a more classical design (personal observation).

4. Conclusion

There is a tremendous need for trials in children affected by epilepsy. Some specific controlled trials are performed in school-age children with focal epilepsy, but the younger age group and epileptic encephalopathies are neglected. As a result, infantile epilepsies remain 'therapeutic orphans' despite the fact that they represent the most deleterious conditions. Considering the complexity necessary to improve the feasibility of AED trials in children without decreasing their quality, extrapolating data from adults to children in the limited field of efficacy within focal epilepsy, and innovative methodologi-

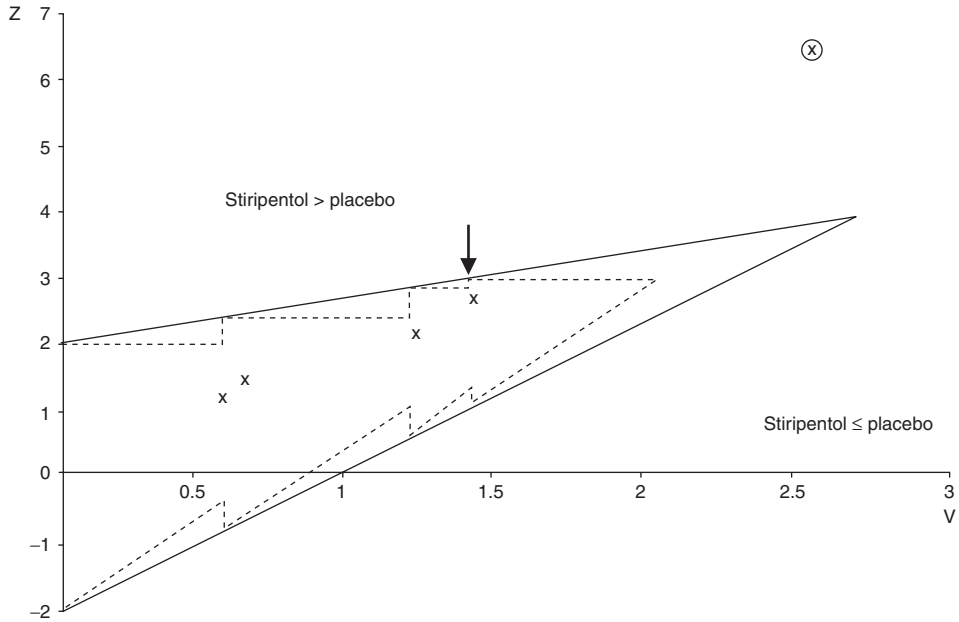

Fig. 1. Triangular test uses a sequential plan represented on a graph with two perpendicular axes corresponding to two statistics Z and V. The statistic Z (vertical axis) summarizes the current difference between the experimental treatment and control. The statistic V (horizontal axis) represents the quantity of information accumulated since the beginning of the trial. It reflects both the cumulated number of patients and the number of observed events, and it will thus always increase as the study progresses. Two additional straight lines intersect and define an asymmetric triangular area with two external stopping boundaries. At each interim analysis, the two statistics Z and V are calculated from the accumulated data and define a datapoint reported on the graph. The consecutive datapoints plot a broken line named the 'sample path' going from left to right. The study is continued as long as the sample path remains within the two boundaries and is stopped when the sample path crosses one of the boundaries. The conclusion of the study depends on which boundary is crossed: experimental treatment better than control for the upper boundary, experimental non-different or inferior to control for the lower boundary. The equations for each of the boundaries are specific for a trial and depend on prespecified α (two-sided) and β error rates, on the expected benefit from the experimental treatment over control and on the expected rate of events in the control group of the study. In the present example, the trial conducted with stiripentol in Dravet syndrome,[16] the triangular test method would have allowed to detect a benefit of stiripentol from the 25th included patient instead of the 41st, and from 1.5 years of trial duration instead of 2.5 years. The black arrow points to the stopping time provided by the triangular test method. The circled cross represents the sample path at stopping time of the original study.

cal approaches should be considered, both to protect the children and to facilitate the evaluation of necessary medications in the whole paediatric population with pharmacoresistant epilepsy.

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