Outcome measures for the assessment of new antiepileptic drugs

• Fred Schobben, Yechiel Hekster and Barbara van Zwieten-Boot

Introduction

For the approval of any new medicinal product three requirements are essential: quality, safety and efficacy. In discussions on the value of a new drug the first item is often underestimated, but the quality of design and production of any new product is a basic requirement. A good quality of a product means a guarantee for reproducible properties of the drug in its final formulation, including bioavailability, both during the pre-registration and the post-registration period and a safeguard against varying amounts of contaminating substances, throughout all produced and forthcoming production batches and during storage up to the approved expiry date. The safety and efficacy parameters should be seen in positive balance: the therapeutic gain must always be more important than the disadvantages: toxicity, the burden of treatment, adverse drug reaction and potential risks.

The assessment of these criteria and the decision making is based on the dossier, that is prepared by the pharmaceutical company applying for registration. The picture from such a dossier may sometimes differ from the properties of the product per se, as acknowledged by the medical professionals or from the scientific literature. This indeed can lead to a situation that a licence is refused for an indication that is widely recognised and for which the drug is successfully applied. However, once a product has been accepted in one of the EC countries, the Mutual Recognition Procedure might facilitate the broad acceptance of such a product.

There is increasing international cooperation and coordination of activities on the field of assessment of medicines, both regarding the registration phase and post marketing surveillance. Examples of this cooperation are found at the European level in the European Medicines Evaluation Agency (EMEA), the Committee on Pharmaceutical Medicinal Products (CPMP) and on a global level in the International Conference on Harmonization (ICH), a forum where authorities and industry from Europe, USA and Japan try to harmonize requirements for registration. This type of cooperation increasingly leads to joint decisions.

Guidelines

In the judgement of the data in such a dossier the authorities and their experts often rely on guidelines, that are relevant for medicinal products in general or for specific therapeutic classes or even for subgroups of patients. Some of these guidelines, especially those issued by the national or supranational authorities, have been set up after extensive consultation of the pharmaceutical industry. For the registration of antiepileptic drugs some guidelines are of special importance:

In the first place the Guideline on medicinal products for the treatment of Epileptic Disorders [1], in which special emphasis is given on the development plan of a new antiepileptic drug and the choice of

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Abstract
For the approval of any new medicinal product quality, safety and efficacy are essential requirements. This manuscript focusses on the clinical development programme. For the investigation of antiepileptic drugs some international guidelines are of special importance. They are based on the knowledge of many experts and can be seen as a consensus on minimal requirements; deviations must be thoroughly justified.
In phases II and III, usually randomised, double-blind add-on studies versus placebo in patients with therapy-resistant seizures are used to get an impression of the efficacy and certain safety issues. A clear dose-response relationship may be a good indication for efficacy. However, assessment of safety of the new product in add-on studies is difficult. Therefore comparative phase III monotherapy studies versus established antiepileptic drugs are essential to confirm the results obtained in add-on studies and are needed for a proper judgement of the efficacy/safety balance.
The percentage of reduction of seizure frequency has played a dominating role as efficacy criterium. Nowadays preference is being given to the percentage responders. Which parameter is the most relevant for the given group of patients and what change is considered clinically relevant must be thoroughly argued. The definition of responder should focus on major benefit for the patients involved.

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trials and type of patients involved and also the Guidelines for clinical evaluation of antiepileptic drugs, edited by the professionals in the epilepsy field itself, covered by the International League Against Epilepsy [2].

Other important guidelines are: Clinical Investigation of medicinal products for long-term use [3 4], focussing on maintained efficacy but especially on safety during long-term use, and Clinical investigation of medicinal products in children [5], with major attention for safety. Relevant are also the Guidelines on good clinical practice; the EEC guideline from 1990 [6] is now being replaced by a corresponding guideline from the ICH [7]. These guidelines put major emphasis among others on methodology and documentation in order to improve the protection of patients and the credibility of data.

Although these guidelines are designed to give merely guidance in the planning and execution of investigations, their impact is much broader. Because they are based on the knowledge of many experts they may be seen as a consensus on minimal requirements.

This means that deviations from these guidelines must be thoroughly justified by authoritative experts.

Clinical studies

The evaluation process involves the chemical-pharmaceutical data on a product, the pharmacological-toxicological investigations and the clinical studies. In this contribution major emphasis will be laid on the clinical development programme of a potential antiepileptic drug. As usual the pre-registration clinical studies are divided into the well known phases I, II and III studies. Although in some drug development plans phase II and III studies tend to merge, we will follow the classic scheme here.

PHASE I

These studies include the first administration to man, and are mainly set up to evaluate the safety of a new product. Based on all available knowledge, from in vitro properties, results of animal studies to human experience with related substances, escalating single dose experiments are started in healthy volunteers, followed by multiple dose studies.

In this phase pharmacokinetics and metabolism are studied in order to confirm that the preceding animal experiments have been the correct model to examine potential toxicity, and to choose the right dosing regimen for the experiments to come.

The next step is to evaluate the safety in epileptic patients. There may be a considerable difference in the dose tolerated by healthy volunteers and by patients, e.g. because of induced liver enzymes and drug interactions in the latter group. The studies are generally performed as rising dose add-on trials. These studies should also include pharmacokinetic investigation to detect interference of enzyme induction, inhibition, interactions or the role of metabolites. In this phase a preliminary impression of efficacy and certain safety issues may be obtained, in non-blind or single blind comparison with placebo. The design of the studies may be dedicated to this problem: for instance a single dose study in photosensitive patients or a multiple dose add-on study in patients with frequent seizures. For antiepileptic drugs to be administered for considerable periods of time, also in learning children, it is considered of importance to get an early impression of potential influence on cognitive functions. Therefore psychometrics tests in volunteers may be performed during the initial stages of development.

PHASE II

In this phase it should become clear whether the product has anticonvulsant properties in man. Usually randomized, double blind add-on studies versus placebo in patients with therapy-resistant seizures are used to demonstrate this. Here the use of an active comparator is hardly feasible; instead inclusion of various fixed doses of the new product is preferable. A clear dose-response relationship suggests a very solid indication for efficacy. This type of study must define the dose-range for the forthcoming phase-III efficacy studies. Studies on interactions with other anti-epileptic drugs may be helpful in defining appropriate dosage selection or adjustment policy of concomitant treatment for the next stage of development. Specific attention for effects on cognitive function in patients is warranted as they may be quite different from healthy volunteers.

PHASE III

Proof of relevant efficacy can only be given by randomised, double blind studies in comparison with an established antiepileptic drug. Add-on studies in patients with defined seizure types of stable frequency might prove that the drug has an efficacy comparable to already established antiepileptic drugs, and an acceptable level of toxicity. However, only if the new product is clearly superior to the reference drug with regard to seizure control will this be accepted as proof of clinically relevant efficacy. Proof of equivalence with the comparator in add-on studies is difficult: the study design and conduct have to fulfill a large number of conditions (see Guideline on Biostatistical methodology in clinical trials)[8]. Moreover assessment of safety of the new product itself in add-on studies remains difficult.

Therefore monotherapy studies are essential to confirm the results obtained in add-on studies in a much broader population and to define the ultimate dosage recommendation. Placebo control in these studies would enable to judge the absolute effect of the new drug but several ethical issues are raised, and it appears to be very difficult to include patients in such studies. Comparative monotherapy studies in previously untreated patients are of major importance. In addition, monotherapy studies are essential to get a clear view on the intrinsic toxicity of the new compound. These studies are therefore required for a proper judgement of the efficacy/safety balance.

The acceptance of lamotrigine showed differing viewpoints from European authorities and experts in this respect. Early approval was based on a number of add-on studies, that showed a statistically significant reduction of seizures compared to placebo. This beneficial result was considered of limited magnitude by others, and it was therefore not accepted as definite proof for a positive efficacy/toxicity balance. Subsequently a number of monotherapy studies in newly diagnosed patients versus well-known compar-

ator drugs were completed and some long-term 'secondary monotherapy' studies, in which lamotrigine was initially added to the existing therapy, that was sequentially withdrawn. In these studies efficacy appeared to be equal to comparators and reassuring data on long term safety were obtained. These data were accepted as the convincing evidence.

The duration of the double-blind treatment period depends on the seizure frequency of the patients included but should be at least 2-3 months. In order to demonstrate efficacy during long-term treatment studies on continued treatment are necessary. In these studies special attention must be paid to tolerance, for instance by comparison of average dosages after several periods of follow-up, and to withdrawal effects. For sufficient data on long-term safety studies should cover a minimum treatment of 100 patients during 1 year, or ideally 300-600 patients during 6 months.

In special cases the requirement of monotherapy studies may be dropped. However, there must be a strong justification to do so. The recent history of introduction of new antiepileptic drugs has shown some examples: vigabatrin and felbamate. Vigabatrin showed an outstanding reduction of seizures in a number of add-on studies in partial epilepsy. Felbamate has been registered on a number of phase II studies and only one add-on placebo controlled phase III trial. This was due to its impressive efficacy in patients with the Lennox Gastaut syndrome; this syndrome is notorious for its therapy resistent seizures. The reduction in atonic seizures, which can lead to severe wounding of the patients, was striking. This property led to the authorization of felbamate in 1995 by the European concertation procedure, for restrictive use in this type of epilepsy. Because of the increasing number of reports on serious haematological and hepatic side effects the drug was only approved for use in refractory cases [9].

PHASE IV

Although these trials formally fall outside the scope of this paper, some remarks may be useful. During this phase in general other seizure types than those focussed on during the pivotal efficacy trials are studied. Also attention is paid to treatment of specific age groups although children may already have been involved in phase III studies in special seizure types. Studies in children are especially important to show safety and to reveal potential impact on learning, cognition and growth.

During phase III patients with kidney- or liver-dysfunction are generally excluded from participation, and this will mostly result in contra-indications for use in those patients. Specific studies are needed to prove safe dosage regimens for those patients; depending on the properties of the drug, pharmacokinetic studies may be sufficient.

Specific studies on the use of drugs during pregnancy are only performed in exceptional cases and have not been done in epilepsy; after registration data on this topic deserve to be collected. Post Marketing Surveillance of new drugs is an essential part of the development, and will be mainly focused on long-term safety and rare adverse effects.

Criteria of efficacy

Although the percentage of reduction of seizure frequency has played a dominating role as efficacy criterium for many years, the most relevant issue is how much the patients benefit from treatment. Therefore preference is being given to the percentage responders, where responders are defined by a change considered as clinically relevant improvement. This definition must be given before the start of the trial. It may concern a change in seizure frequency, seizure free interval or seizure pattern or severity relative to the baseline observation period. A change of seizures may not be the only relevant response; attention should also be paid to assessment of functional capacity, well-being and/or cognitive functioning, though they are not the primary endpoints for approval. Which parameter is the most relevant for the given group of patients must be thoroughly argued, preferentially by a group of experts. They should also decide what change is considered clinically relevant. For out-patients with a drivers licence years of freedom of seizures may be the appropriate goal, while for institutionalised handicapped patients the number of days without post-ictal drowsiness might be a good choice. The percentage responders should be calculated for the new drug, comparator and/or placebo. It must be balanced against the percentage of patients with a clinically relevant deterioration. As the percentage responders varies considerably among studies, analysis based on number to treat may be a better approach of absolute benefit [10]. Analyses should be done on an intention to treat basis. Special attention is asked for drop-outs; are they caused by lack of efficacy or by side effects? Even their follow up is very important: do they show withdrawal or rebound effects?

Side effects

Due to the nature of most studies, estimation of side effects attributable to the new drug is difficult. Experience during recent years has learnt that for some new drugs add-on studies did not correctly reveal the side effect pattern. Therefore lack of sufficient monotherapy studies hampers the evaluation of adverse events. For a good judgement of the efficacy /toxicity balance these studies are essential. When the mechanism of action of a new compound is known this may help to evaluate some of the side effects and to interpret the relevance of toxic effects in animal studies. Unfortunately this is not the case for most antiepileptic drugs.

Overall judgement

After all relevant data on quality, safety and efficacy have been evaluated a general judgement on approval has to be made by licensing authorities. For each aspect there are of course minimal requirements, and a number of remaining questions may be easily solved. Major discussions almost always concern the balance between the clinical benefit and the (potential) toxicity. In order to make a proper judgement it is of utmost importance that the pivotal clinical studies make use of relevant outcome criteria. The choice of these criteria must be thoroughly argumented. As discussed here, the percentage responders, according to

pre-defined criteria, in comparative add-on and monotherapy studies, is considered a major parameter. The criteria should be based on expert knowledge on the patient and his disease, and should focus on major benefit for the patient. For proper judgement of the side effect pattern, and hence the efficacy/toxicity balance, monotherapy studies are considered of great importance. Although opinions on some of these topics differ, the common goal of industry, authorities and medical practitioners remains to get available effective and safe medicaments in order to improve the treatment of patients suffering from epileptic seizures.

With that idea in mind it is difficult to justify that certain clinical trials are only set up to satisfy the regulatory authorities and that other trials have to be performed later on to convince the clinical practitioners of the useful place of the new drug among the existing therapies. This gap in design and outcome parameters between pre-registration and post- registration trials, as it is generally perceived, needs to be bridged as soon as possible; ongoing discussions between scientists and clinicians from the parties involved may be helpful.

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