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REVIEW

Evaluation and registration of adverse events in clinical drug trials in migraine

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Tolerability of a drug should be regarded as important as its efficacy. In all four phases of drug development evaluation of adverse events is important. Recommendations for assessment of adverse events in acute and prophylactic clinical drug trials in migraine are given. Tolerability may be indirectly assessed using measures of general well-being and eight such tools are presented. Finally, recommendations for reporting of adverse events are given. □*Migraine, adverse events, assessment, reporting*

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Introduction

In 2000 the Clinical Trial Subcommittee of the International Headache Society published its second edition on controlled clinical trials in migraine (1). The overwhelming emphasis was on efficacy. Adverse events (AEs) were mentioned only in passing. From clinical practice it is well known that AEs are a major problem in treating migraine with drugs, especially in preventive therapy, often leading to discontinuation of the drug. In randomized clinical trials (RCTs), however, with topiramate 200 mg AEs resulting in discontinuation of treatment were similar in patients with migraine (21–44%) (2–4) and in child, adolescent and adult patients with epilepsy (8–28%) (5, 6), despite slow titration in both cases. The aim of these guidelines is to try to fill the current gap between clinical practice and controlled RCTs by improving the external validity of clinical trials with regard to AEs. Evidence-based medicine is based mainly on RCTs and systematic reviews, and these sources of information should reflect clinical experience.

Optimizing the evaluation and reporting of AEs should be considered in the planning phase of an RCT in migraine. One may ask the question: 'what is special about migraine?'. A migraine attack is a special time-limited event with headache and associated symptoms. Adverse drug effects can mimic some symptoms of the migraine attack; conversely, migraine symptoms may mimic AEs (see below). The time period for analysis of AEs after drug intake can therefore be important.

Terminology surrounding AEs is frequently confused, with individual terms often used loosely and interchangeably. AEs are unfavourable outcomes

that occur during or after the use of a drug or other intervention, but not necessarily caused by it. An adverse effect, side effect or adverse reaction is an AE for which the causal relationship between the intervention and event is at least a reasonable possibility (7). In clinical trials we are interested in any adverse effects of the studied intervention, but it is usual to collect and report information about all AEs without prejudging causality, which can also be assessed if appropriate.

Safety refers to serious adverse effects, whereas tolerability usually refers to medically less important (i.e. without serious or permanent sequelae) but unpleasant adverse effects. These can affect quality of life and willingness to continue treatment. AE intensity is usually rated as mild, moderate or severe. In addition, their impact can be rated using general well-being/quality of life measurements and with headache specific questionnaires (8–13).

In practice, the overwhelming number of RCTs will be planned for efficacy, and what one can hope for is that a similar standardized method of evaluating and reporting AEs in these trials will make meta-analyses possible.

Drug development

It is important to recognize that different phases of drug development give different information on AEs.

Human pharmacology—Phase 1 trial

These are placebo-controlled trials, in which few individuals are treated. They may provide a signal of potential adverse effects, particularly those related to dose and drug interactions, and also adverse effects not predicted from animal studies. They are usually done in healthy volunteers, although it is desirable to use a relevant population, matched for age and sex, and preferably of migraineurs.

Therapeutic exploratory—Phase 2 trial

These are randomized, placebo-controlled trials in which AE assessment is of equal importance to efficacy assessment. This may be the first use in a patient population rather than healthy volunteers, so may reveal AEs specific to that population. These trials should give information on the nature, frequency and intensity of common AEs and possibly dose-related adverse effects, but are unlikely to give information on rare AEs.

Therapeutic confirmatory—Phase 3 trial

These are randomized, placebo-controlled trials that may use active comparators. They are generally larger than exploratory trials, often multicentre and sometimes involving several countries. These trials should give information on common AEs, and their larger size should give better precision in estimates of outcomes. For AE comparisons of active treatments, clinically comparable doses should be used. They may detect differences in AE profiles between two drugs, and ethnic and cultural influences within and between populations. They can also indicate patient preference between two active treatments, based on efficacy and tolerability. They may still exclude significant sections of the eventual exposed population, limiting extrapolation and generalizability of results. It is desirable to include adequate representatives of the whole population likely to receive the drug after approval.

Therapeutic use—Phase 4 trial

These trials are a requirement of regulatory agencies (6–12 months' duration for acute use, 1 year for prophylactic), but may also be done for other reasons.

They are designed primarily to study long-term safety and tolerability, not efficacy. They can provide additional information on tolerability with repetitive use, rare AEs, and adverse effects due to drug interactions. Many therapeutic confirmatory trials (Phase 3) go into an open-label extension phase to assess therapeutic use. Patients who are not tolerant of the treatment, or who derive inadequate benefit from it, during the double-blind phase will not enter the open phase. The population enrolled is consequently enriched in patients who tolerate and respond to the treatment, and although this reflects clinical practice, results require cautious interpretation and extrapolation to the general population.

Study design

For subjective outcomes, blinding is mandatory. A placebo control defines the study population and is necessary to establish the background rate of AEs, against which those of the test treatment(s) can be compared (14). It can also allow comparisons between study centres or countries even when the background rate of events differs.

A cross-over design has only within-subject variation, and is the most sensitive design to pick up differences between treatments, but can be compromised by drop-outs and loss of blinding, and risk of carry-over effects. Parallel design is more simple and avoids these confounders, but requires more patients due to presence of both intra- and interindividual variation.

Assessment of adverse events

Acute trials

Record AEs for the same time period as for the efficacy assessment.

At home: Ask patients to report AEs for each time point at which efficacy is recorded. Use a standard open question (e.g. 'Have you experienced any unusual or abnormal event or symptom? If so, what was it?') and, where relevant, ask directly about specific AEs of interest (e.g. 'Have you experienced chest pain?'). Ask for detail about intensity (using a scale of 0–10 or mild/moderate/severe) and, if possible, duration of each reported AE.

Follow-up visit: Follow-up with investigator checklist within 1 week—or where there is a well-defined pharmacokinetic/pharmacodynamic relationship use 5× half-life of drug if this is greater. Go through the patient report, check for omissions, code AEs with the patient, using a standard system (e.g. COSTART) prespecified in the protocol. Ask for the patient's general clinical impression (why? efficacy, tolerability?) and whether the patient would use the treatment again (no/perhaps/certainly) and why (efficacy, tolerability?). Perform a clinical examination, as specified in the protocol, to identify changes or abnormalities in vital signs and laboratory tests. For continuous variables, significant change in the individual should be prespecified, as, for example [coefficient of variation for the variable (CV)]: $2\sqrt{2}$ CV% for two-sided change; 2.3 CV% for one-sided change.

Prophylactic trials

At home: Ask patients to report AEs on a daily basis, using a standard open question ('Have you experienced any unusual or abnormal event or symptom? If so, what was it?'), and, where relevant, ask directly about specific AEs of interest (e.g. 'Have you experienced chest pain?'). Ask for detail about intensity (using a scale of 0–10 or mild/moderate/severe) and duration of each reported AE. When no symptoms are experienced, the patient should be asked to indicate so, rather than not reporting anything. It may be helpful to use electronic recording of data (e.g. via internet), which would also facilitate prompting for missed data.

Follow-up: Go through the patient report, code AEs with the patient, using a standard system (e.g. COSTART) prespecified in the protocol. Perform a clinical examination, as specified in the protocol, to identify changes or abnormalities in vital signs and laboratory tests.

Alternatively, one could use a self-reported screening instrument for AEs, as has been used successfully in epilepsy (15).

End of treatment visit: Ask for general clinical impression (why? efficacy, tolerability?), and whether the patient would use the treatment again (no/perhaps/certainly) and why (efficacy, tolerability?), based on the whole treatment period.

A follow-up visit or contact (e.g. telephone) is recommended. The timing depends on the treatment studied—1 month may be appropriate.

In the event of discontinuation, complete the end of treatment visit.

In order to mimic the clinical situation, flexible dosage regimens with slow titration, as used in the topiramate trial programme (2–4), can if possible be recommended. In epilepsy, slower titration has been shown to reduce withdrawals due to treatment-emergent AEs (16).

An investigator assessment of the relationship of an AE to drug use may be required for serious AEs, but is probably of little value for non-serious AEs, and not recommended in absence of regulatory requirements.

Additional assessments

Tolerability may be indirectly assessed using measures of patient well-being. A number of tools have been evaluated and shown to be valid and reliable for assessing patient well-being. Some are generic and some disease specific. Generic questionnaires are suitable for comparisons between study populations and different diseases, whereas disease-specific questionnaires may be more sensitive in assessing symptoms over time associated with a single-dose or multiple-dose regimen. These questionnaires may be immediate, or retrospective (24 h to 4 weeks), and data can be captured either on paper, or using electronic devices, such as computers and hand-held devices. Most have been developed to assess efficacy rather than tolerability.

Generic

- SF-36 *(36-item Short-Form Health Survey)* (9)
- SF-12 QoLQ *(12-item Short-Form Health Survey)* (17)
- MSEP *(Minor Symptoms Evaluation Profile)* (8)
- PGWBI *(Psychological General Well-Being Index)* (18, 19)
- SSAP *(Subjective Symptoms Assessment Profile)* (20)

Specific

- MSQ *(Migraine Specific QoL Questionnaire)* (11, 12)
- HDI *(Headache Disability Inventory)* (10)
- HImQ *(Headache Impact Questionnaire)* (13)

SSAP is a subjective symptoms inventory. PGWBI and MSEP assess the general well-being of the patient without asking specific headache-oriented questions. Different dimensions of the patients' general well-being are demonstrated. Improvements in headache symptoms will be reflected by improvement in general well-being, which also reflects the overall assessment of both efficacy and tolerability (21, 22).

Most of these assessments provide good indicators at the time of administration, but very few like MSEP has been demonstrated to be sensitive enough to detect small differences over time (8, 23). The MSEP has been shown to discriminate between symptoms induced by different classes of drugs, as well as differences in the subjective well-being of normotensives, borderline hypertensives and hypertensives, as well as migraineurs vs. controls (8).

Although statistically significant changes may frequently be seen, a change of $\geq 10\%$ is generally considered to have clinical relevance.

Reporting of adverse events

It is not uncommon for AEs to be carefully assessed and recorded during clinical trials, but subsequently to be poorly or incompletely reported, making an evaluation of their impact within the trial, and comparison with other trials or meta-analysis, unsatisfactory or impossible.

For each treatment arm, report:

- number of patients with one or more AE;
- number of patients with any serious AE;
- number of patients withdrawing because of an AE;
- number of patients with individual/specific AEs that are of prespecified interest or are common or otherwise likely to affect tolerability;
- intensity of specific AEs;
- details of all serious AEs, including possible causation;
- detailed table of individual AEs. This should be for all AEs or all AEs by organ system, rather than only those occurring in a particular percentage of patients or with a statistically different frequency from another treatment arm.

Consistent reporting of outcomes is essential.

- Numerator and denominator should always be reported. Percentages should not be used if $n < 50$.
- It is recommended that both relative and absolute summary statistics (relative risk or odds ratio *and* attributable risk or number needed to harm/number needed to prevent) are used.
- Outcomes should be reported consistently in one direction (e.g. drug vs. placebo or drug vs. active control) throughout.
- Presentation of results as means should be used only when the distribution approximates to normal.

The abstract should include mention of AEs to give a balanced summary and to facilitate identification by electronic searching.

Interpretation of results and influence of confounding

Interpretation of the results should always consider the context of the trial and its external validity.

Patient recruitment

It is essential to report and explain (with reasons) the recruitment procedure. This may differ between centres in multicentre trials, and may influence AE reporting. Report the number or proportion of patients naive to test drug and drug class.

Inclusion and exclusion criteria may limit generalizability.

Study design

Placebo controls are essential for evaluation of AEs in trials with subjective end-points. Subjective end-points are very sensitive to blinding, but blinding may be compromised in cross-over trials, and even parallel group trials if adverse effects are characteristic and identified during informed consent. A trial may be adequately powered to demonstrate a

difference between treatments for efficacy, but remain underpowered to differentiate between AE profiles.

Use of rescue medication in acute trials and acute medication in prophylactic trials can complicate interpretation of AEs.

Responders and non-responders may report central nervous system AEs at different rates (24).

Co-morbidity or underlying disease severity may influence both occurrence and reporting of AEs, as can concomitant drugs in add-on trial designs.

Competing interests

C.D. has been consultant/scientific advisor in advisory boards, clinical trials, investor initiated trials and speakers for Allergan, Almirall Prodesfarma, AstraZeneca, Bristoll-Meyers Squibb, GlaxoSmithKline, Jansen Cilag, Merck, Lilly, Novartis, Ortho-McNeil Pharmaceuticals, Pharmacia, Pfizer, Pierre Fabre. E.L. has received research support, honoraria, consulting fees or hospitality from AstraZeneca, Endo, GlaxoSmithKline, Merk, Ortho-Neil/Jansen. H.M. has been consultant/scientific advisor in advisory boards for Allergan, Almirall Prodesfarma, AstraZeneca, GlaxoSmithKline, Jansen Cilag, Menarini, Merck, Novartis, Pfizer, Pierre Fabre, Schwarz Pharma. PT-H. has been consultant/scientific advisor in advisory boards for Almirall Prodesfarma, Jansen Cilag, Pfizer, Pierre Fabre.

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