Guidelines for controlled trials of drugs in cluster headache

First Edition: International Headache Society Committee on Clinical Trials in Cluster Headache

COMMITTEE MEMBERS

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The present guidelines were developed under the auspices of the International Headache Society (IHS) to facilitate high quality controlled clinical trials (CCTs) in cluster headache. Quality CCTs are the only way to convincingly establish the efficacy of any drug treatment. These guidelines for CCTs are designed mainly to test drug efficacy. For general issues in clinical trials, the reader should consult works on clinical trial methodology (1–4). Here, issues of specific relevance to cluster headache will be emphasized. Previous discussions of related issues, as they pertain to migraine, have been reported (5–9). This paper was modelled after the IHS guidelines for controlled trials of drugs in migraine (10).

Pharmacotherapy for cluster headache is divided into two broad categories: acute treatment and preventive treatment. Acute treatment is given at the time of the attack to decrease the pain duration and severity of an individual attack. Preventive treatment is taken on a daily basis mainly to decrease the frequency of attacks. Trials concerning these two types of treatment require different designs but there are many issues in common. The major issues to be considered are: patient selection, trial design, selection of endpoints, evaluation of results, and data analysis. At the end, checklists are given for drug trials concerning both acute and prophylactic treatments. The recommendations and comments are usually generic for acute and prophylactic therapy. Differences or additions for prophylactic therapy but not for acute therapy are indicated by italics.

The main purpose of these guidelines is to draw the investigator's attention to the problems inherent in drug trials in cluster headache. Recommendations are based on the clinical and research experience of the committee members. Only a few

recommendations are firm, and none should be regarded as dogmas; several alternative solutions to particular methodological problems may be equally appropriate.

The clinical characteristics and natural history of cluster headache have several features which influence the design of CCTs. First, cluster headaches are rare compared with the other primary headache disorders. The lifetime prevalence of cluster headache has been estimated to be 0.07%, but at any given time most people are not in a cluster period (11). Even in multicentred studies, sample sizes are limited by subject availability. Second, there are two major types of cluster headache (12). (We do not address the paroxysmal hemicranias, though they are often included as a type of cluster headache (13, 14)). The episodic type is characterized by daily or near daily attacks for weeks or months followed by pain-free remissions lasting weeks to years. In patients with chronic cluster headache, attacks occur on a daily or near-daily basis for more than one year. Chronic cluster headache comprises from 10 to 20% of all cluster headache (15, 16); it is sufficiently rare as to be very difficult to study. For episodic cluster headache, CCTs should be designed to minimize the effects of spontaneous remissions of the cluster period which tend to attenuate our ability to detect true treatment benefits. Third, individual attacks of cluster headaches are very short in duration, typically lasting less than 1 h. Study designs therefore must be sensitive to the early onset of relief of individual attacks. Fourth, cluster headache shows an overwhelming male predominance; it is therefore virtually impossible to study an adequate number of women with cluster headache as a separate stratum.

In the planning phase of a CCT, a limited number of primary outcome variables should be defined in advance. Pilot studies should be used to select outcome measures which are reliable and valid. (We suggest outcome measures in section 3). Though the dramatic nature of cluster headache attacks and the low placebo response rates (17, 18) make open and single-blind trials informative, these trials should be regarded as hypothesis-generating. The results should always be subsequently assessed in CCTs.

After pilot studies, the drug should be compared with placebo, and efficacy relative to established drugs should also be evaluated in CCTs. As discussed below, multi-arm comparative trials are logistically difficult because cluster headaches are relatively rare. The comparison of a new treatment with an established one often poses problems. Sometimes the new drug is found better than an established drug, but in many trials (of migraine for example) two drugs are found to be not significantly different. When the results of these trials are reviewed critically (19, 20), it often becomes apparent that the sample sizes are too small for realistic differences between treatments to be detected (inadequate statistical power).

Ethical considerations

Controlled trials in cluster headache should be performed, as for any drug trial, in accordance with the Declaration of Helsinki II. Because the pain of cluster headache is often excruciating and effective therapy exists, the treatment under study must have strong promise. This concern is partially mitigated by the relatively short duration of cluster attacks and the lack of known long-term sequelae of untreated attacks.

The use of placebo in cluster headache trials is justifiable in CCTs when the scientific questions cannot be solved without the use of placebo (see sections on trial design). Escape medication should be offered in acute trials, though quite often attacks may spontaneously remit before escape medication can be used. Prolonged periods of treatment with an ineffective prophylactic agent (or placebo) should be avoided. Preliminary studies are required to optimize dose and determine required duration of treatment before benefits begin.

General considerations of drug trials dealing with treatment of the acute attack

In trials dealing with the treatment of the cluster headache attack one should be aware that the pain is not always stable. It typically reaches a peak within a few minutes and the vast majority spontaneously resolve within 30 to 120 min (IHS criteria 15–180 min) (12, 15). Atypical patterns of evolution may pose problems regarding the timing of administration of medication (either early or when the attack is fully developed), and in evaluation of results.

General considerations of drug trials dealing with cluster headache prophylaxis

If active treatment appears to be effective in comparison with a baseline period, the improvement noted may be due to the natural history of episodic cluster headaches, a disorder which spontaneously remits. Therefore, comparative trials must be placebo-controlled. The numbers of patients needed will be large enough to require multicentre trials. Under-powered studies are not worth doing.

1. Selection of patients

1.1. Cluster headache definition

Recommendations: The diagnostic criteria of the IHS should be used (Cephalalgia 1988:8 Suppl 7;1–98) (12). Both episodic and chronic cluster headache patients may be studied, but results from one group cannot necessarily be generalized to the other.

Comments: We recommend strict adherence to the IHS criteria. There are people who do not meet the IHS criteria, who are diagnosed as having cluster headache, treated accordingly and respond appropriately. For clinical drug trials, however, requirements are more rigid than in clinical practice. Those rare patients who have paroxysmal hemicrania or syndromes that combine features of cluster headache with features of migraine or tic doloureux should not be enrolled in CCTs of cluster headache. The identification of homogeneous groups more than offsets the small incremental difficulty in recruiting subjects and the loss of generalizability.

Although acute attacks of episodic and chronic cluster headache are similar, they might respond differently to acute therapy. Ideally, either episodic or chronic cluster headache should be studied, but because of the small number of patients the two may be pooled for studies of acute therapy if the treatment responses are not significantly different in the two groups.

Because some prophylactic medications may alter the course of the disease, differentiation is necessary between episodic cluster headache, chronic cluster headache evolving from episodic and chronic cluster headache unremitting from onset.

1.2. Interval headaches

Recommendations: Patients with interval headaches of other types need not be excluded if the patients can readily distinguish the cluster headaches.

Comments: The inclusion of patients with interval headaches is permitted if, as is usual, patients are able to differentiate these headaches from cluster headaches. In a study conducted at home, the headache diary should differentiate between the two types of headache by simply asking the patient: ''Is this a typical cluster headache attack?'' When identified, interval headaches may simply be recorded by the number of days per 4 weeks. Stabs or twinges of pain that sometimes occur between, preceding or during attacks of cluster headache may be recorded on a daily or weekly basis, but only full-blown attacks should be treated.

1.3. Frequency and duration of attacks

Recommendations: Attacks of cluster headache should occur from one every two days to five per day (typically one to three per day). The attacks should last from 15 min to 3 h. The average duration of attacks must be longer than the expected time to onset of the drug.

Comments: The IHS gives a maximum frequency of eight per day and a minimum duration of 15 min for cluster headaches (12).

As these limits are approached, it becomes difficult to differentiate between cluster headache and paroxysmal hemicrania. Chronic paroxysmal hemicrania is characterized by attacks which are more frequent (more than eight per day) and shorter in duration (less than 30 min) than those of cluster headache (12). An episodic variant of this disorder has been described but is not included in the current IHS classification (14). Patients with paroxysmal hemicrania invariably respond to indomethacin but not often to other cluster headache treatments (14, 21). Patients with headache attacks of less than 30 min duration which occur more than five times daily should be excluded from cluster headache treatment trials. Very few patients will be excluded by this additional restriction.

1.4. Duration since onset of the cluster period

Recommendations: Patients should not be enrolled unless a prior cluster period has occurred; they should not be enrolled for their first bout of episodic cluster headache. Patients may be enrolled if they meet IHS criteria for chronic cluster headache unremitting from onset, i.e., attacks occur for more than one year without remission or with remissions of less than 14 days.

For prophylactic treatment trials, the expected duration of the episodic cluster period after randomization should be at least one month after start of therapy. The expected duration of the cluster period must be longer than the expected time to onset of action of the drug and the preselected follow-up period.

Comments: *Both chronic and episodic cluster headache warrant prophylactic therapy. There is great potential for error in attributing cessation of the cluster period to the study drug rather than to the natural remission period of episodic cluster headache. However, spontaneous remissions should occur at equal rates with active drug and placebo.*

The duration of the patients' typical cluster period must be tabulated. In general, patients should not be enrolled in the study unless their cluster period is expected to continue for at least one month beyond the time of randomization and therapy. However, if the effect of therapy is expected to have a rapid onset, a period less than one month may be acceptable. Requiring a longer expected duration of a cluster period would make enrollment more difficult and the generalizability of study findings would be limited to those with long-duration periods of cluster headache.

1.5. Age at onset

Recommendations: There need be no age limitations in terms of diagnosis.

Comments: Cluster headache may begin at any age (22).

1.6. Age at entry

Recommendations: Age at entry should be determined by medication safety.

Comments: A special protocol will be required for children (under the age of 18). Patients with cluster headache over the age of 65 are increasingly subject to cerebrovascular and cardiovascular diseases and other illnesses that may increase the hazard of experimental drugs.

1.7. Gender

Recommendations: Both male and female patients are acceptable.

Comments: There are more men than women in the cluster headache population. Efforts should be made to recruit female as well as male patients. Special caution is advised to exclude pregnant women from treatment trials. Sexually active women should be using effective contraception.

1.8. Concomitant drug use

Recommendations: Concomitant therapy for the acute attack is not permitted but, after the window for efficacy assessment is complete, escape therapy should be offered.

During prophylactic treatment trials, concomitant acute therapy should be permitted. Abortive therapies cannot be withheld when pain is excruciating. No other prophylactic drugs should be taken for the period of active study. Drugs not used for cluster headache are permissible if they have no known effect on cluster headache, no known interaction with study medication, and the dose has been stable for three months.

Comments: *Allowing acute treatment in prophylactic trials has an important influence on study endpoints. The duration and severity of cluster attacks become difficult to study if acute treatment is effective. Attack frequency becomes the primary endpoint variable. Ideally, cluster headache prophylactic medication should be discontinued for an adequate wash-out period for prophylactic studies.*

Patients may be taking drugs for prophylaxis without important benefit. Unresponsiveness to medication may be due to inadequate dose, short duration of use, or other factors. These patients may be withdrawn from their medication and, after an adequate wash-out period, randomized in a preventive treatment trial.

1.9. Exclusions

Recommendations: The following groups are excluded—those who abuse drugs, including headache treatments and alcohol (DSM

III criteria); those who are allergic to compounds similar to the study medication; those who are taking antipsychotic or antidepressant medication during the prior month; those with relevant physical or psychological illness; those who are pregnant or who do not use adequate contraceptive methods.

Comments: Patients who occasionally use sedatives or minor tranquillizers, and who use contraceptive drugs, need not be excluded. Such exclusions would too severely limit the study population. On the other hand, it is desirable to eliminate people who take excessive drugs for any reason or who abuse alcohol.

2. Trial design

2.1. Blinding

Recommendations: CCTs should be conducted using a double-blind design.

Comments: Open or single-blind designs are only advisable in early safety studies. Apart from these trials, drugs used for the treatment of cluster headache can only be reliably evaluated in randomized, double-blind trials.

2.2. Placebo control

Recommendations: Drugs used for the treatment of cluster headache usually should be compared with placebo. When two active drugs are compared, a placebo-treated control group should also be included. When a trial is designed solely to determine if a new drug is better than a standard drug, there is no need to include placebo.

Comments: While the placebo response rates in migraine treatment trials usually range from 20 to 40%, the placebo response rates in cluster headache therapy are lower (17, 18). In efficacy studies, drugs should usually be compared with placebo. When an experimental drug is found to be not significantly different from a standard treatment, that does not establish the efficacy of the experimental agent. The lack of significant differences may be a consequence of poor statistical power or inadequate study design; demonstrated improvement relative to baseline in both areas may be a consequence of spontaneous remission or the placebo effect. Ideally, both drugs should also be studied relative to placebo. To refer to the previous efficacy of an established drug in other trials is not adequate; the methodology in the present study may be insensitive to the benefits of treatment. Using historical controls is methodologically fraught with error and not recommended.

2.3. Crossover vs parallel studies

Recommendations: Either the crossover or parallel paradigms can be used for studies of acute therapy.

A parallel design is recommended for studies of prophylactic therapy of cluster headache.

Comments: A crossover design is more likely to reveal true differences with a limited sample size (23). There is little risk of carryover effects (i.e., the effects of the first drug persisting into the treatment period of the second drug) in acute treatment, but a period effect (i.e., differences between the first and second treatment periods) using the crossover design has been observed in some trials of headache medication (24). If patients are asked to participate in two independent treatment phases of the crossover design, the participation rate may fall and the drop-out rate may rise. The investigator will therefore pay a price by studying a less representative sample. In addition, resources will be wasted on patients who complete the first phase of the study and then drop out. A parallel group design avoids these problems, but makes less efficient use of study participants with this uncommon condition. In balance, the crossover design for the acute therapy trials is favoured. The simple AB, BA design is not adequate for assessing carryover effects. Alternative designs include the AB, BA, AA, BB treatment groups or three arm study designs have been recommended (25).

The crossover design has major drawbacks for prophylactic treatment trials in cluster headache. First, there is a need for a wash-out period between treatments with a high probability of headache recurrence. As a result, there may be a loss of blinding, a high drop-out rate or both. In addition, by prolonging the period of study, spontaneous remission rates would increase. As previously discussed, these remissions would make it more difficult to identify true benefits of treatment.

2.4. Stratification

Recommendations: Stratification should be considered for gender and cluster headache type (episodic vs chronic).

For prophylactic drug trials of episodic cluster headache, subjects should be stratified by the present duration of the cluster period.

Comments: Stratification is intended to yield groups that are matched for characteristics which may influence treatment results. This is recommended for gender because of the relative paucity of females with cluster headache. Response to therapy and subsequent course may differ between chronic and episodic cluster headache patients, warranting stratification based on this feature.

Stratification by the duration of the cluster period prior to randomization (e.g., 2 weeks) is intended to yield groups with similar rates of spontaneous remission. This will prevent differences in duration of the

cluster period from confounding study results by ensuring that groups are comparable.

2.5. Randomization

Recommendations: For crossover and parallel group studies, treatment order should be counterbalanced (active agent vs placebo).

Comments: Because patients are recruited for cluster headache trials over extended periods and episodic cluster attacks occur over a limited period, a rolling method of enrollment and randomization is recommended, i.e., randomization should occur in relatively small blocks. Again, spontaneous remissions would lead to misclassification.

2.6. Duration of treatment periods for prophylaxis (not applicable for acute therapy)

Recommendations: *Treatment periods of at least two weeks should be used for prophylactic therapy. The period should be defined based for both the time required to optimize dose and the interval required for treatment effects to occur.*

Comments: *For prophylactic therapy, a period of at least 2 weeks is required because the efficacy of some drugs develops gradually (i.e., may need weeks before becoming fully effective). A predefined period for assessing treatment effects should be selected based on results of pilot studies. Though only prolonged benefits are clinically relevant, spontaneous remissions make prolonged observation problematic.*

2.7. Dosage

Recommendations: In assessing any new drug, a wide range of possible doses should be tested to define the dose–response relationship. The doses used in phase III trials should be selected based on efficacy and safety.

Comments: Ideally, the dose regimen should be derived from dose-finding studies which establish the therapeutic range for both the amount of drug administered and the blood levels of the drug. Dose-finding studies must examine both side effects and therapeutic effects. Some of the pharmacokinetic studies can be done in non-patient controls. Therapeutic ranges have not been systematically established for any drug used in the treatment of cluster headache.

The choice of dose is one of the crucial factors in determining the chances for a successful completion of a CCT. As long as the pharmacological background for the efficacy of certain drugs remains unknown, the choice of doses in trials is determined by balancing efficacy and side effects. Since information

about dose–response relationships in cluster headache is lacking, there is no solution to the problem. Instead, good clinical judgements should be used. Dose-ranging trials, i.e., dose titration on an individual basis, are an alternative method which merits consideration.

2.8. Route of administration

Recommendations: In early trials to establish efficacy, various routes of administration may be considered, but rapid absorption is critical in acute treatment trials.

Comments: For acute therapy, pharmacokinetic studies in volunteers should establish that absorption is rapid before embarking on a controlled trial. Given the short duration of cluster attacks, rapid absorption is essential in acute therapy.

2.9. Time of administration

Recommendations: In acute CCTs, the drug should be given as early in the attack as possible, but not before pain has become at least moderate (headache pain rating: none [0], mild [1], moderate [2], severe [3], excruciating [4]).

Comments: Because of the rapid onset of cluster headaches, the need for early therapy is obvious. Waiting until pain is at least moderate ensures that a full-blown attack is being treated and that improvement of at least two points on the pain scale can occur.

2.10. Frequency of treatment (for acute attacks) (not applicable for prophylactic therapy)

Recommendations: As a maximum, no more than one attack per 24 h should be treated with the study medication. To avoid carryover effects, the minimum interval between treated attacks should be at least five half-lives.

Comments: Medication used for one attack might have a carryover effect when attacks are treated in close proximity. The interval between treated attacks should be based on the pharmacokinetics and pharmacodynamics of the drug, particularly time of maximum blood level and biological half-life. As 95% of a drug is dissipated in five half-lives, waiting at least five half-lives between treated attacks seems prudent. If interval cluster attacks occur between experimental treatments, treatment with appropriate standard agents is permissible but must be recorded. Other studies may evaluate treatment of multiple attacks per day, as sometimes occurs in clinical practice.

2.11. Number of acute attacks to be treated (not applicable for prophylactic therapy)

Recommendations: Two to four attacks may be treated within an individual.

Comments: The treatment of multiple attacks per subject should increase the discriminative power of CCTs. Because attacks of cluster headache are closely spaced, treatment of multiple attacks will not greatly prolong the trial. However, repeated intake of a placebo should be limited because of the low response rate and consequent loss of ''blinding''. The analytic strategies must be appropriate for managing multiple attacks within an individual.

2.12A. Escape therapy for acute attacks

Recommendations: For *acute therapy trials*, escape therapy should be allowed as early as possible after the interval of expected effectiveness. The interval must be determined based on pilot testing with the study drug.

Comments: For practical and ethical reasons, patients should be allowed to take escape medication after the interval of expected benefit has passed. For example, if the study drug is parenterally administered and usually works within 15 min, an escape medication could be used after 30 min. Need for escape medication is a useful secondary endpoint for assessing efficacy. After the escape medication is offered, outcome scores from the time of administration should be carried forward; additional assessment of experimental treatment is not possible.

2.12B. Symptomatic treatment during prophylactic therapy

Recommendations: *For trials of prophylactic therapy, patients should use their usual symptomatic treatment for acute attacks (unless there is a contraindication or interaction), but the types of acute therapy should be kept constant for each patient during the trial. Symptomatic treatment should be taken only when the pain has reached at least a moderate degree.*

Comments: *It is ethically inappropriate to withhold acute treatment during prolonged periods of cluster headache. It is neither ethical nor practical to standardize the symptomatic treatment used by patients during a prophylactic drug trial. Delay in taking symptomatic therapy until the pain is of at least moderate degree will ensure the reporting of the true attacks rather than twinges of pain or other minor prodromal symptoms that often, but not invariably, signal the onset of an attack.*

When patients are clearly using ineffective symptomatic therapies, the investigator should prescribe the most suitable acute treatment.

2.13. Control visits

Recommendations: Patients should contact the study centre within one to two days of using acute therapy and should be seen at least monthly during *prophylactic therapy.*

Comments: Relatively frequent visits are important in order to check the headache diary and encourage the patient's continuation in the trial. In dose-ranging trials, patients should be seen every one or two weeks. If patients are seen monthly, diaries should be returned to the investigator for review weekly to ensure timely appropriate recording of data.

3. Evaluation of results

3.1. Attack report form

Recommendations: A simple report form suitable for answering the main objectives of the trial should be used.

Comments: Complicated report forms with detailed descriptions of symptoms of the attack may be difficult for patients to fill out during cluster headaches. The headache diary should be suitable for evaluating the primary and secondary endpoints selected for study (see below). (Secondary interpretation by investigators, if performed, should be of efficacy, independent of the patient's assessment). In addition, information about adverse events should be recorded.

3.2. Severity of headache

Recommendations: In acute treatment trials, the intensity of head pain should be noted by the patient just before the drug intake and at frequent intervals during the period when treatment benefits are expected. For example, if treatment effects peak 10 min after administration, ratings might be made at 5, 10, 15 min, and every 15 min thereafter. A rating should be completed at the time an escape medication is taken. An ordinal scale may be used: 0=no headache, 1=mild headache, 2=moderate headache, 3=severe headache, 4=excruciating headache. Alternatively, a visual analog pain scale may be used.

Comments: The recommended ordinal scale takes into account only pain intensity. Pain relief scales have the advantage of using pain at the time of treatment as a reference. The functional consequences of the attack may not correspond to the degree of pain intensity. Functional status may be rated as a secondary parameter.

The patient is asked to rate a single value, intensity of pain, by "integrating intensity over time'' and stating a global assess-

ment of the degree of pain. It is difficult to give simple or standardized rules for patients to use. One has to be aware that patients are probably rating the maximum intensity of the pain. Note that intensity of pain increases at the beginning and decreases at the end of the cluster period. *Prophylactic therapy may decrease intensity of pain as well as frequency of attacks.*

3.3. Time to meaningful relief

Recommendations: In acute treatment trials, time to relief may provide a useful secondary endpoint. Patients should note the time of onset of the attack, turn on a stop watch when taking the test drug and turn it off when experiencing meaningful relief. When an attack relapses within one hour, even if the treatment seemed initially effective, it should be considered the same attack.

Comments: This method allows calculation in minutes of the time to meaningful relief, the time interval from taking the test drug to the end of the attack. Because cluster headaches are of short duration, time to relief provides a critical expression of efficacy. Proper analysis of this endpoint requires survival analysis. This strategy has not been used as of the time of this writing. It is mentioned here because of its intuitive appeal, not because of established utility.

The rule given for temporary disappearance of headache is arbitrary, but practical. *Prophylactic therapy may decrease duration as well as frequency of attacks.*

3.4. Frequency of headache (for prophylactic therapy)

Recommendations: *The number of attacks should be recorded on a daily basis irrespective of their duration.*

Comments: *Note that the frequency of attacks increases at the beginning and decreases at the end of the cluster period. The number of responders can be expressed as those with a significant reduction in attack frequency during treatment compared with the baseline period. The ratio of number of attacks per month or per week in groups using the active drug versus placebo may be used to compare groups.*

3.5A. Primary efficacy criterion for acute therapy

Recommendations: For *acute therapy*: the primary efficacy criterion is the proportion of attacks effectively stopped within set time intervals before escape therapy. Efficacy is defined as reduction of intensity to no headache or mild headache from moderate, severe, or excruciating. A secondary efficacy criterion is the time to meaningful relief.

If an attack stops within a time frame but recurs within one hour, it is considered a treatment failure.

Comments: Attacks of cluster headache may occur on more than one occasion during 24 h, therefore, recurrence of headache after resolution is not necessarily a treatment failure. However, recurrence of headache within one hour of remission suggests inadequate therapeutic efficacy and, for practical purposes, can be considered a treatment failure.

If a drug is effective in bringing a rapid resolution of the attack, but the attack relapses because of the short duration of action of the drug, repeated intake of the same drug may be optional; evaluating this mode of treatment requires a particular study design. Patients with recurrences must be randomized to receive active agent or placebo. The speed of efficacy or ''stop watch'' design may be useful in comparing two or more therapies that are approximately equal in ultimately terminating an attack.

3.5B. Primary efficacy criteria for prophylactic therapy

Recommendations: *Frequency of attacks per week should be the main efficacy parameter.*

Comments: *Based on pilot studies, a preselected time interval after optimizing treatment should be used to assess number of attacks per unit time. This interval from onset of treatment should be long enough to allow treatment effects to develop but short enough to minimize the risk of spontaneous remissions. Similarly, the time interval of active evaluation should be long enough to provide a salient estimate of attack frequency but short enough to minimize spontaneous remissions.*

3.6. Associated autonomic symptoms

Recommendations: The presence of autonomic symptoms should be recorded at the times of primary interest.

Comments: Autonomic symptoms associated with cluster headache are not usually distressing but study of their course following therapy may afford insight as to the drug's mode of action.

3.7A. Escape therapy for studies of acute treatment

Recommendations: The need for escape therapy after intake of the test drug can be used as a secondary outcome measure.

Comments: This parameter is usually well correlated with the patient's judgement of the efficacy of the test drug.

3.7B. Symptomatic treatment of acute attacks during prophylactic therapy

Recommendations: *The number of attacks that required treatment (e.g. oxygen or other medication) per week should be recorded.*

Comments: *There is no satisfactory way of quantifying the use of symptomatic therapy because of the different drugs or modalities used by patients. Within-patient comparisons, the drug consumption or oxygen use can be used as a secondary assessment parameter, whereas its use is dubious for between-patient comparisons.*

3.8. Global evaluation of therapy

Recommendations: A simple verbal scale should be used to indicate the level of patient satisfaction with treatment: poor, moderate, good, excellent.

Comments: This criterion may be one of the most clinically relevant, taking into account both efficacy and tolerance. The latter is not used as a primary measure.

4. Statistics for acute therapy

The recommended primary endpoint in acute treatment trials, the proportion of attacks which are relieved by a preselected time point, can be analysed with standard statistical methods. In calculations of sample size, the investigator should estimate the placebo response and define the difference to be detected. Standard statistical methods can be used for analysis of assessment parameters in both crossover and non-crossover trials; time to relief requires survival analysis (26, 27).

A period effect has been found in some crossover trials and should be dealt with appropriately.

Confidence intervals for differences are recommended in order to fully inform the reader of the results of the trial (28). A statement that two drugs are comparable without giving confidence intervals is unacceptable.

5. Statistics for prophylactic therapy

Calculations of sample sizes in prophylactic parallel group trials, based on frequency of attacks, have been published (29).

The parallel design comparisons between groups can be made either as comparisons during the treatment periods or as comparisons of changes from baseline. The latter is conceivably more powerful, but analyses have so far only shown a marginal increase in power. In parallel trials the use of the baseline value as a covariate should also be examined.

Confidence intervals for differences are recommended (28) in order to inform the reader fully of the results of the trial. A statement that two drugs are comparable without giving confidence intervals is unacceptable.

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