Clinical Investigation of Anti-Anginal Medicinal Products in Stable Angina Pectoris

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Additional Notes: This note for guidance is intended to provide guidance on clinical investigations to determine the value of medicinal products in preventing attacks of angina pectoris and to increase symptom limited exercise capacity, irrespective of the nature, mode of action, or route of administration of these products.

It should be read in conjunction with Part 4 of the Annex of Directive 75/318/EEC, as amended, and other guidelines for conducting clinical trials. This version replaces the previous 1987 guideline: Anti-anginal drugs.

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CLINICAL INVESTIGATION OF ANTI-ANGINAL MEDICINAL PRODUCTS IN STABLE ANGINA PECTORIS

INTRODUCTION

This note is intended to provide guidance on clinical investigations to determine the value of medicinal products in preventing attacks of angina pectoris and to increase symptom limited exercise capacity, irrespective of the nature, mode of action, or route of administration of these products. It is intended for the investigation of medicinal products to be used in patients with stable angina pectoris. This comprises angina induced by exercise or by other stimuli, but not unstable angina pectoris.

This note for guidance should be read in conjunction with Part 4 of the Annex to Directive 75/318/EEC as amended, and guidelines for conducting clinical trials, especially those on:

- Pharmacokinetic Studies in Man
- Clinical Investigation of Medicinal Products for Long-Term Use
- Dose Response Information to Support Product Authorisation
- Biostatistical Methodology in Clinical Trials
- The Extent of Population Exposure to Assess Clinical Safety for Medicines Intended for Long-Term Treatment of Non-Life-Threatening Conditions

The clinical profile of such a medicinal product needs to be studied in an acute stress testing setting, i.e. with provocation of anginal attacks due to cardiac ischaemia, which is assumed to represent the conditions of normal practice. Valid data are only likely to be obtained if sufficient account is taken of such factors as the pronounced placebo effect in angina pectoris, the substantial variation in the nature and severity of symptoms, and the subjective character of ‘chest pain’.

2. CRITERIA OF EFFICACY

As the assessment of the effect of antianginal medicinal products based on clinical measurements alone is as yet considered too unreliable because of the possible influence of uncontrolled variables, it has become accepted that measurements of exercise capacity using standardised exercise testing should be, in spite of an intrinsic amount of variability, the major criteria of efficacy. In addition to its objective character, it is assumed that improved exercise capacity may be a surrogate for the patient benefit in terms of better quality of life. Moreover, exercise testing provides evidence that the relief of angina and increased exercise capacity are mediated by an anti-ischaemic effect. In addition, clinical evidence of symptomatic improvement should also be provided in the major therapeutic trials.
2.1 Exercise based variables

2.1.1 Exercise capacity

Exercise testing provides a wide array of variables, all of which may contribute to the assessment of the antianginal effect. The assessment of total exercise capacity at trough which is defined as the residual effect at the end of the dose interval, is the major efficacy criterion for antianginal medicinal products. Total exercise capacity (total exercise time or total workload performed) is probably the most meaningful measurement that can be obtained from exercise testing, and thus it should be considered, by itself, as a primary endpoint in therapeutic clinical trials. Total exercise capacity can be defined as the maximal duration or workload of exercise which can be performed by the patient in the setting of a standardised exercise test. The reasons for interrupting exercise should be related to symptoms (e.g. Borg score ≥ 3) and signs of myocardial ischaemia. With adequate study conditions (low intra-individual variability of the initial results, adequate patient selection), the variability of consecutive measurements is relatively low, thus ensuring acceptable reproducibility.

However, other exercise variables should be used for an adequate characterisation of the effect on antianginal effect in addition to total exercise capacity. A consistent result in these exercise variables should be demonstrated before accepting an effect on exercise capacity.

2.1.2 Time to the onset of angina

Time to the onset of angina has its limitation derived from the subjective nature of pain. Furthermore a significant amount of treated patients might have no limiting angina after treatment or might be limited in their exercise capacity by reasons other than angina.

2.1.3 Time to ST segment depression

Time to 1 mm ST segment depression in the left precordial leads is a more objective variable and it is indicative of an anti-ischaemic effect which is an important fact in antianginal medicinal product assessment. Nevertheless, at present, its extrapolation in terms of clinical benefit for the patient is unknown.

The above three variables can be considered to be relevant to therapeutic effect, and all of them should be measured in therapeutic trials. They must show consistency or at least no major contradiction between them in order to conclude efficacy of a new medicinal product.

2.1.4 Other exercise variables

Additional exercise variables can also be measured. These include the rate-pressure product, the magnitude of ST depression, gasometric measurements, and radionuclideographic evidence of myocardial hypoperfusion or ventricular dysfunction induced by ischaemia.

2.2 Anginal pain / consumption of short acting nitrates

Frequency, intensity and duration of anginal pain as well as the concomitant use of short acting nitrates should be documented. Whereas this variable is not considered to be a primary endpoint, it is highly relevant as a secondary endpoint in both short-term and long-term studies.
2.3 Quality of life
Quality of life measurement can provide valuable information about the effect of therapy on the general health status.

2.4 Morbidity and mortality
At present, there is no requirement to prove beneficial effect on these variables in order to obtain a marketing authorisation, although any effects on cardiovascular and total morbidity and mortality should be evaluated. This should be done in particular if there is a reasoned suspicion that a new medicinal product might have detrimental effects on these parameters (See also section on safety).

2.5 Ischaemic episodes
Ambulatory recording of ischaemic episodes may give supportive evidence for the efficacy of the medicinal product tested.

3. METHODS TO ASSESS EFFICACY

3.1 Exercise testing
Bicycle or treadmill exercise tests should be employed to induce angina. The exercise protocols should be validated and follow the recommendations of international organisations of cardiology. The characterisation of ST segment abnormalities suggesting ischaemia should be based on internationally accepted criteria. At least two standardised exercise tests should be performed at the start of the study. The difference between the tests should not exceed 20%. If patients are included with a larger difference a rationale for this should be given.

Other stress tests should be limited to phase II studies.

Repeated measurements over time, e.g. every 2 to 4 weeks, should be performed.

The physiological testing of the patients must be performed under medical supervision in facilities equipped to treat any cardiac complication.

3.2 Anginal pain
The patient's experience of anginal pain should be recorded in a patient diary as well as the concomitant use of short-acting nitrates. The daily frequency of anginal pain should whenever possible be registered by patients using available log books.

3.3 Quality of life
A quality of life assessment may be considered, provided the questionnaire is validated in the context of the proposed target group.
3.4 Morbidity and mortality
Cardiovascular morbidity and mortality can be measured in specially designed studies, but should always be evaluated and assessed using the pooled data of the (controlled) trials.

3.5 Ischaemic episodes
Appropriate information on the number and duration of ischaemic episodes (either symptomatic or silent) can be measured by standardised ambulatory ECG recording (Holter monitoring) over 48 hours. The tapes should be evaluated using acknowledged equipment.

4. SELECTION OF PATIENTS
The patients included in the studies must suffer from stable angina pectoris on the basis of coronary heart disease, preferably documented by a history of proven myocardial infarction, previous coronary revascularisation or coronary angiography. With regard to dose-finding studies the documentation of unequivocal coronary heart disease is mandatory. Stable angina is defined as anginal exercise pain of more than 3 months duration in the absence of angina at rest or accelerated chest pain pattern.

Patients with a recent (< 3 months) cardiac event such as myocardial infarction, CABG surgery or percutaneous angioplasty should not be included in the studies.

The patients to be included in the study must be capable of exercise testing according to standardised protocols. The stability and reproducibility of the patient’s symptoms and exercise performance are essential to the studies. The symptoms of angina pectoris and the nitrate consumption must have been stable at least during the 2 weeks preceding the study. Any concomitant medication shall have been unchanged during this period of time.

At least in some studies efforts should be made to enrol a study population without concomitant antianginal medicinal product therapy where the investigational product should be given as monotherapy.

Some of the trials should also include patients where the investigational product is given as add on therapy and compared to an acceptable active control and/or placebo. Rescue medication with short acting nitrate should always be allowed throughout the whole trial period.

5. STRATEGY - DESIGN
5.1 Initial studies
5.1.1 Pharmacodynamics
These studies should define the pharmacodynamic properties of the active ingredient and of any active metabolites. The studies should include, when appropriate, data on:
• Haemodynamic effects at rest and during exercise;
• Myocardial oxygen consumption;
• Coronary blood flow/diameter of normal and stenosed coronary arteries;
• Effects on heart rate, rhythm, conduction times and, if necessary, refractory period;
• Effects on renal function and electrolytes;
• Effects on the pulmonary function;
• Effects on the metabolism, particularly of glucose and lipids;
• Neurohormonal effects;
• Platelet aggregation and other rheological effects;
• Vital and laboratory parameters;
• Adverse events;
• Tolerability.

5.1.2 Pharmacokinetics
The kinetics of any active metabolites should also be studied if they contribute to the effects of the medicinal product.

The studies should also provide data in potential at risk patient groups (e.g. the elderly, patients with heart failure, patients with renal or hepatic dysfunction and in slow metabolisers, where applicable).

5.1.3 Interactions
Pharmacokinetic and pharmacodynamic interactions should be investigated primarily with other frequently coadministered medicinal products in the target population, e.g. other antianginal products, antihypertensive agents, medicinal products to treat heart failure, anticoagulant products. Interactions with other substrates of the metabolising isozymes should also be investigated.

5.2 Therapeutic studies
Withdrawal of concomitant antianginal medication prior to randomisation would allow a methodologically proper evaluation of the new antianginal medicinal product as monotherapy.

A run-in period with placebo lasting at least 2 weeks should be considered in order to ensure the stability of the disease. Short acting nitrates are allowable for interruption of angina attacks. Efficacy throughout the whole dosing interval should be proven.

5.2.1 Dose Response studies
Dose Response studies should be randomised, placebo-controlled and double-blinded using at least three dosages to establish the clinically useful dose range as well as the optimal dose. These studies should preferably be designed as parallel group studies and should last at least six weeks.

The results of the dose response studies of a new antianginal medicinal product should provide robust evidence of its efficacy as compared to placebo, including precise quantitative estimates of its beneficial effects.
5.2.2 Main therapeutic studies

The objectives of the main therapeutic studies should be to confirm the efficacy and safety of the product.

These studies should be performed in a randomised, double-blind, controlled, parallel group design. Active controlled studies, of at least 12 weeks duration, should demonstrate comparable efficacy and safety to an appropriate standard therapy. These studies may last even longer in order to allow a comparison with respect to adverse drug reactions as well.

As stated in section 4, some of the trials should also include patients where the investigational product should be given as add-on treatment and compared to an acceptable active control and/or placebo.

6. SAFETY ASPECTS

Results of pharmacoepidemiological studies suggest that the influence of different antianginal medicinal products classes on (cardiovascular) morbidity and mortality may not be alike even though the antianginal effect is comparable. Effects on cardiovascular and total morbidity and mortality should be evaluated on the basis of phase II/III trials.

Long-term data on adverse events must be presented as the medicinal product may be administered for long periods of time. Thus at least 300 patients should be treated for a minimum of 6 months or 100 patients for one year, preferably in controlled trials. All adverse events occurring during the clinical trials as well as morbidity and mortality data must be fully described, assessed and discussed in the context of current knowledge about antianginal medicinal product therapy. Special attention should also be paid to serious adverse events and reasons for treatment withdrawals.

The safety aspects should usually address the following points:

Specific effects such as pro-anginal and pro-arrhythmic effects as well as other cardiovascular effects, withdrawal phenomena and any effects related to rebound phenomena or general effects influencing the function of other organ systems, e.g. through alterations of regional blood flow. Both the time of occurrence and the frequency, severity, relevance and outcome of any adverse events must be documented and discussed.

Special attention should be paid to high risk groups (e.g. heart failure, renal and hepatic failure, etc.) and to possible interactions with other medicinal products.