INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

DRAFT ICH CONSENSUS PRINCIPLE

PRINCIPLES FOR CLINICAL EVALUATION OF NEW ANTIHYPERTENSIVE DRUGS

Signed as a Principle Document

on 2 March 2000

by the ICH Steering Committee

This consensus draft text, agreed by the appropriate ICH Expert Working Group, is transmitted by the ICH Steering Committee to the regulatory authorities of the three ICH regions (the European Union, Japan and the USA) for internal and external consultation, according to national or regional procedures.

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PRINCIPLES FOR CLINICAL EVALUATION OF NEW ANTIHYPERTENSIVE DRUGS

INTRODUCTION

This document provides general principles for the clinical evaluation of new antihypertensive drugs. It describes core principles for the evaluation of antihypertensives that are accepted in the three ICH regions, but some region-specific differences remain. These differences may be harmonized in future, but it is important at present to refer to existing regional guidelines and to discuss the specific requirements with regional regulatory authorities, if required. This document should be considered together with a number of pertinent ICH guidelines:

E1 : The Extent of Population Exposure to Assess Clinical Safety.

E3 : Structure and Content of Clinical Study Reports.

E4 : Dose-Response Information to Support Drug Registration.

E5 : Ethnic Factors in Acceptability of Foreign Clinical Data.

E6 : Guideline for Good Clinical Practice.

E7 : Studies in Support of Special Populations : Geriatrics.

E8 : General Considerations for Clinical Trials.

E9 : Statistical Principles for Clinical Trials.

E10 : Choice of Control Group in Clinical Trials.

E11 : Clinical Investigation of Medicinal Products in the Pediatric Population.

There are, in addition, existing regional guidelines or draft guidelines.

CPMP: Note for Guidance on Clinical Investigation of Medical Products in the Treatment of Hypertension.

FDA: Proposed Guidelines for the Clinical Evaluation of Antihypertensive Drugs.

MHW: Guideline for the Clinical Evaluation of Antihypertensive Agents.

1. GENERAL PRINCIPLES FOR THE ASSESSMENT OF EFFICACY

The primary basis of assessment of efficacy of antihypertensive drugs is the effect of the drug on systolic and diastolic blood pressures. In the past the primary endpoint of most studies was diastolic blood pressure. Although all drugs to date have reduced both systolic and diastolic blood pressures, the recognition of isolated or predominant systolic hypertension as a significant and remediable risk factor demands explicit

evaluation of the effect of a drug on systolic blood pressure. Many clinical trials of many interventions (including low and high dose diuretics, reserpine, and beta-blockers, usually as part of combination therapy) have shown consistent beneficial effects on long-term mortality and morbidity, most clearly on stroke and less consistently on cardiovascular events. Whether some drugs or combinations have better effects than others on overall outcomes or on particular outcomes is not yet known.

Formal mortality and morbidity outcome studies are not ordinarily required for approval of antihypertensive drugs and the kind of active control mortality and morbidity studies that would be convincing is not well defined. Results of a large number of on-going outcome studies could affect this policy and modify requirements. It should be noted that, even if an antihypertensive effect has been proven, a significant concern about a detrimental effect on mortality and/or cardiovascular morbidity might lead to a need for outcome studies.

2. STUDY POPULATION

The patient population studied with a new antihypertensive should include a broad range of patients with essential hypertension. Most patients will be in the mild to moderate range. Studies of patients with both diastolic and systolic hypertension are expected. More severe hypertension should also be studied. Patients with relevant concomitant illness (such as diabetes mellitus and coronary heart disease) should be included unless the drugs they need would interfere with the study; e.g., for patients with heart failure standard treatment requires use of one to several agents affecting blood pressure that could have pharmacologic actions similar to the study drug.

In general, patients with target organ damage secondary to hypertension should not be included in placebo-controlled trials of more than very brief duration, although such patients can be included in active controlled trials. Patients from relevant demographic subsets should be studied, including both men and women, racial/ethnic groups pertinent to the region, and both young and older patients. The very old or "fragile elderly," i.e., patients >75 years old, should be included. In general, all population subsets should be included in the same studies, rather than conducting studies in subgroups. This facilitates comparisons across subsets in the same environment. An exception would be severity subgroups, where study designs could be different for different severities. Patients with secondary hypertension, isolated systolic hypertension, and hypertension during pregnancy, and children with hypertension should be studied separately, if specific indications for use in those populations are being sought.

3. ASSESSMENT OF ANTIHYPERTENSIVE EFFECT

3.1. Studies to Assess Antihypertensive Effect

The primary endpoint of studies to assess antihypertensive effect is the absolute change at the end of the dosing interval (trough) from drug-free baseline blood pressure compared to the change in the control group. As a secondary endpoint effects can also be assessed with respect to pre-defined response criteria. In general, the effect on blood pressure at the end of the study is the primary endpoint, but the

time course of the onset of the effect is also of interest; this can be defined by examining trough response each week or every two weeks in some studies. The effect on blood pressure and the relationship of the response to dose should be characterized in short-term studies (4-12 weeks), whose short duration allows for use of a placebo control. Long-term (six months or more) studies should also be carried out to demonstrate maintenance of efficacy and to look for withdrawal effects.

Because blood pressure readings (except perhaps ABPM readings) are subject to systematic error (bias), because spontaneous changes in blood pressure can be large, and because the effect of active drugs is often small (diastolic blood pressure change of 4-5 mm Hg more than placebo), studies conducted in a blinded fashion and with placebo controls are essential (See ICH E10). In general, short-term studies should be placebo-controlled. Dose-response studies and studies using an active control drug as well as placebo are strongly encouraged. Controlled randomized short-term studies of various designs can be useful in demonstrating effectiveness, for example (See also Appendix):

A) Single fixed-dose vs. placebo

B) Optional titration (based on response) vs. placebo

C) Forced titration vs. Placebo

D) Fixed-dose, dose-response vs. placebo (can use forced titration to reach the randomly assigned fixed maintenance dose)

E) Any of the above designs with an active control drug

Long-term studies to show efficacy (and which are also needed for assessment of long term safety) would usually use active controls, preferably with a placebo-controlled randomized withdrawal study at the end of treatment to establish assay sensitivity (See ICH E10) and assess possible withdrawal effects. Another long-term active control trial design that could support assay sensitivity would be one in which patients are initially randomized to three treatments (test drug, active control drug and a placebo), with the placebo only maintained for short time (e.g., one month). A long-term open exposure followed by a placebo controlled randomized withdrawal could also show long-term efficacy.

The effect of the drug over the duration of the dosing interval has generally been evaluated in recent years with ABPM studies (which can incorporate dose-response elements and an active control), but studies that measure blood pressure at approximate peak and at trough (pre-dosing) blood levels can also be used. Specific requirements vary among regions. Additional information may be obtained from self (home) measurement of blood pressure with the help of automatic devices, but validation of the device used is necessary. If peak and trough blood pressure effects differ substantially, a more frequent dosing interval should be studied. The trough/peak ratio should be evaluated. Although strict rules (e.g., placebo-subtracted trough/peak at least 50%) have been suggested, interpretation of these ratios has generally been flexible. The principal concern is that there needs to be an adequate blood pressure control late in the dose interval, without an excessive fall in blood pressure at peak resulting from a desire to have a long dose interval (e.g., to gain a once daily dosing claim for a short - acting drug).

Conditions of blood pressure measurement should be well described and standardized with respect to time of day, patient position and specific measurement procedures.

3.2. Pharmacodynamic Studies

The pharmacodynamic properties of antihypertensive drugs should be characterized. Studies should be performed to evaluate such properties as hemodynamic effects, renal effects, and neurohumoral effects. In general, it is useful to characterize the magnitude, dose-response, and time-course of these effects. These studies should usually be placebo-controlled.

3.3. Dose Response Relationship

The dose-response (D/R) relationship for favorable (blood pressure) and unfavorable effects of anti-hypertensive drugs should be well-characterized through randomized fixed-dose, D/R studies. In these studies, a greater number of dose groups will provide a better D/R assessment. If possible, at least three doses (in addition to placebo) should be used. Although trials usually use a randomized parallel fixed-dose, D/R design (See ICH E4), some studies could utilize a placebo-controlled titration design, appropriately analyzed, to narrow the range of doses to be studied in fixed-dose studies, and to characterize individual D/R relationships. Either or both of these designs can provide evidence for anti-hypertensive efficacy. These D/R studies (See ICH E4) should characterize critical parts of the D/R curve, allowing identification of the lowest dose with some useful effect, a dose on the steep part of the D/R curve, and a dose beyond which further effects are absent or small (maximum useful dose). If there is a positive D/R slope, a D/R study can show effectiveness even without a placebo, but it may provide little information on the value of the lower doses (which may then need further study). A D/R study may be uninformative if all doses show equal effects.

3.4. Comparison with Standard Therapy

The need for studies comparing the new drug with current standard therapy varies among regions but comparative studies are of interest in all regions. In order to assess antihypertensive efficacy, these trials need to document assay sensitivity through a placebo arm or a terminal placebo-controlled randomized withdrawal phase. For the short-term studies, a 3-arm design (test drug, active control drug, and placebo) may be particularly helpful as a study that not only supports efficacy but also makes a comparison with standard therapy. If the effect size (vs. placebo) is unusually small, it can be helpful to know whether this was the result of the study population, or other study features (test and control drugs both have small effect vs. placebo), or the drug (active control drug has a larger effect than test drug compared to placebo). For longer-term comparative studies, where concurrent placebo-control is not possible, the approaches to demonstrating assay sensitivity described in Section 3.1 should be considered.

4. ASSESSMENT OF SAFETY

ICH E1 suggests that a database of about 1500 patients (300 - 600 for 6 months, 100 for 1 year) is usually sufficient for chronically administered drugs, but as suggested in

that guideline, this may be too small for the very long, very wide exposure in an asymptomatic population intended for antihypertensive drugs.

In addition to the usual safety assessments, attention should be paid to excessive fall in blood pressure (hypotension), especially on standing (orthostatic hypotension), and rebound phenomena. Depending on the particular drug and other observations, studies of effects on heart rhythm or cardiac conduction, coronary steal effects, effects on risk factors for cardiovascular disease (e.g., blood glucose, lipids), and effects on target organ damage are of interest.

5. CO-ADMINISTRATION WITH OTHER ANTIHYPERTENSIVES

As antihypertensive treatments are often used in combination, it is important to study the efficacy and safety of the new drug in this situation. Information on combination use can be obtained in formal factorial studies and in combined use in the course of long- and short-term clinical studies. Specific requirements regarding clinical co-administration studies may vary among regions.

Studies in patients with inadequate blood pressure control on other agents will provide information on the effect of the test drug when added to other agents (add on studies). Studies in which additional drugs are added to the test drug to achieve an adequate response may also be useful.

6. FIXED COMBINATION PRODUCTS

There are two approaches to the combination studies needed to obtain safety and efficacy data to support fixed combination products. It is essential to consult with regional regulatory authorities regarding the specific data needed to support the specific indications.

6.1. Factorial Study

In a factorial study, placebo, and one or more doses of the test drug T and another drug D are studied alone and in the combination in a short-term randomized controlled trial. Such a trial can be used to show that the combination has a greater effect than either drug alone. Most informative for identifying the appropriate dosages for a fixed combination is a factorial D/R study in which several doses of each drug, e.g., a test drug T and another drug D, and their combinations are compared, as shown below.

Placebo	T_1	T_2	T_3
D_1	T_1D_1	T_2D_1	T_3D_1
D_2	T_1D_2	T_2D_2	T_3D_2
D_3	T_1D_3	T_2D_3	T_3D_3

This design reveals D/R relationships for the test drug and other drug alone and in combination with each dose of the other treatment and may support one or more fixed combinations. These studies reveal "response surface" relationships that use data from all groups. It may be necessary to study separately the low doses and low dose combinations to establish their specific usefulness.

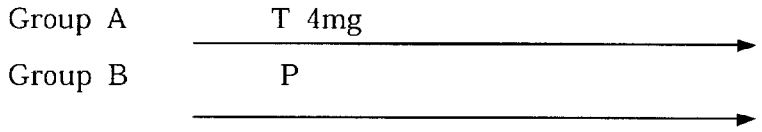
6.2. Studies in Non-responders to Each Drug

The safety and efficacy of combinations can also be assessed by examining the effect of the combination in patients failing to respond to both of the single drugs, e.g., diastolic blood pressure > 90 mmHg on that component. In some cases, regional authorities only require trials in patients failing to respond to one of the components.

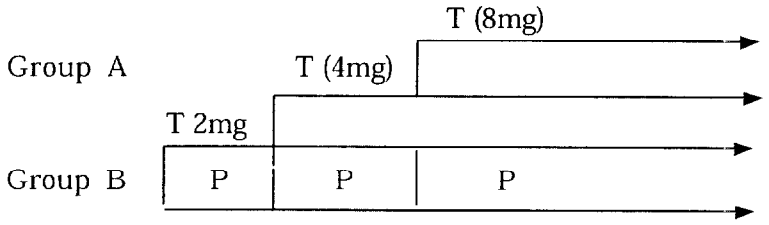
APPENDIX

SHORT-TERM STUDY DESIGNS (T: Test Drug P: Placebo)

A. Single fixed-dose vs. placebo

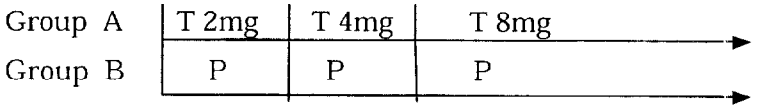


B. Optional titration (based on response) vs. Placebo

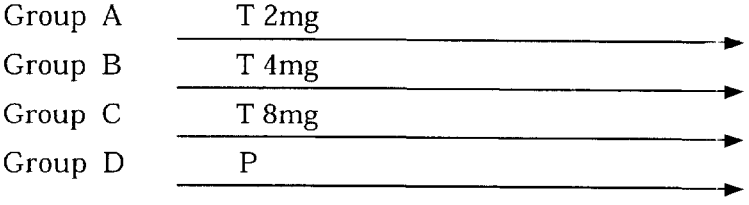


( ):If needed to reach goal

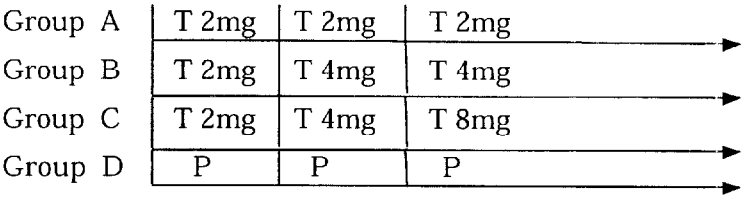
C. Forced titration vs. Placebo



D. Fixed-dose, dose-response vs. placebo (can use forced titration to reach the randomly assigned fixed maintenance dose)



or



E. Any of the above designs with an active control drug