CHAPTER 38

Principles for Evaluation of Pharmacologic Agents

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"New medicines and new methods of cure always work miracles for a while" is a statement attributed to William Heberden. This chapter represents an attempt to amplify the implications of this statement insofar as drug trials in general are concerned and, in particular, clinical trials of pharmacologic agents for the treatment of benign prostatic hypertrophy (BPH).

General Principles of Drug Evaluations

Although a number of clinical trials in the literature are of high quality, a careful reviewer notes many deficiencies in design, conduct, analysis, or presentation of results. Most such studies related to clinical drug trials are in fact only pilot studies, as they are composed of selected patients and are neither blinded nor controlled. This type of study generally serves simply as a preliminary investigation, yielding information only as to what pharmacologic agents should be studied and over what period of time; it gives some idea as to how many patients will in fact be necessary to properly investigate whether a particular drug is efficacious for the condition under study. Most investigators would agree that an ideal clinical trial of a pharmacologic agent for treatment of a particular condition should satisfy certain general criteria.5,10 It should 1) exhibit a lack of bias, 2) include an adequate number of subjects, 3) use appropriate and sensitive methods of evaluation, 4) be conducted under double-blind conditions with a placebo, and 5) be statistically validated.

Specific Considerations

Elimination of Bias

It is obvious that the elimination of conscious bias does not constitute a problem for any reputable scientist. However, unconscious bias can occur, either in the assignment of patients to a particular treatment group or in the assessment of responses. Randomized prospective double-blind studies (see below) virtually eliminate this potential problem. If a study is not randomized and/or double-blind, its validity can be considerably increased if the assessments are done by individuals other than those who actually assigned the patients to the treatment groups.

Sample Size

Many clinical trials do not consider sample size carefully enough and thereby turn out to lack the ability to detect clinically important effects of fairly substantial magnitude. An excellent summary of the theoretical considerations has recently been published.6 Ideally sample size should be determined with the aid of a statistician. There are three primary considerations: 1) the natural history of the condition under study; 2) the magnitude of improvement expected as a result of the therapeu-
tic intervention; and 3) the desired level of statistical significance.

**Appropriate and Sensitive Methods of Evaluation**

Appropriate and sensitive methods should be used to evaluate the effects of treatment in order to obtain data on which to base an adequate answer to the primary question under consideration. Ideally, these methods of evaluation will yield objective data in a form that can be easily analyzed statistically. Subjective data (e.g., symptoms) are generally difficult to quantify and analyze. Symptoms that can be exactly quantified are a statistician's delight; more often than not, however, it is necessary to attach artificial grades to the severity of various symptoms and analyze changes in these.

**Double-Blind Placebo-Controlled Studies**

A prospective randomized double-blind study is the ideal method to determine the clinical efficacy of a therapeutic intervention. Such a design virtually eliminates bias and, with an adequate sample size, ensures as much as is possible that the results obtained are due to factors other than sampling variability in the group under consideration. A double-blind study, in which the subject and the investigator are unaware of the identity of the treatment, ideally compares the drug under consideration to a placebo. There are obvious ethical considerations that pertain to the use of a placebo in a drug trial, particularly if there is a standard therapy that is clearly superior to placebo. However, especially in protocols that use subjective criteria for assessment, it has long been recognized that improvement may occur in up to 35% of placebo-treated patients. This may be a result of true improvement that occurs as a consequence of the natural history of the condition under study, or it may be a result of the placebo effect itself. In general, the placebo effect can be boosted by a very positive and enthusiastic attitude on the part of the treating physician, by the length of time spent with the patient, and by an in-hospital-type regimen. Ethical considerations demand that a patient in such a study be told that his chances of receiving placebo are 50% and that a placebo is equivalent to no pharmacologic treatment at all. Such knowledge by the patient, in the author's opinion, tends to decrease the placebo effect on subjective symptomatology and helps to better define the natural history of the condition under consideration, although it also decreases the number of patients willing to enter a particular study, especially if it is long term. Unblind studies, in which both the investigator and the patient know the treatment being received, are certainly easier to perform from the standpoint of patient recruitment, but unconscious bias is a problem. Single-blind studies with placebo, in which only the investigator knows which therapy the subject is receiving, lessen the chance of patient bias, but are still subject to unconscious bias by the investigator. In any study in which a placebo is employed, it is obvious that the appearance of the placebo and its dosage schedule must be the same as the drug under consideration. It is likewise ideal to eliminate any other factor that would enable the patient to ascertain whether he is in fact receiving medication or placebo. Unfortunately, most if not all clinically useful pharmacologic agents have side effects. It is impossible to build into a placebo the potential side effects of the therapeutic agent under consideration without making it something other than an inert compound. Familiar examples of this problem include placebo-controlled trials of anticholinergic agents for detrusor hyperreflexia or the frequency–urgency syndrome. Another example would be the difficulty inherent in finding a suitable placebo for a study with intravesical dimethylsulfoxide (DMSO).

**Statistical and Clinical Significance**

Determination of the statistical significance of objective parameters is not usually a problem in a placebo-controlled study. Existence of a placebo group should eliminate statistical errors that might otherwise occur because of the variability in results of a particular test and because of improvement that occurs as a result of the natural history of the disease. To ensure statistical validity, some mechanism must be included in the study for ensuring patient compliance in taking the medication or placebo. This generally consists of having the patient record his dosage schedule and returning the unused medication at the termination of the study or at various points during the study. Subjective variables are extremely difficult to quantify.