Editorial

Cardiovascular Drugs: Experience of the Drug Efficacy Study (DES)

PRIOR to 1962 the only legal requirement for marketing a new drug was adequate evidence of safety. The Kefauver-Harris Amendments Act of 1962 altered the original 1938 law to require that valid evidence also must be provided to support the claims of therapeutic efficacy. The FDA, suddenly faced with the task of evaluating the large number of drugs marketed between 1938 and 1962, sought the assistance of the National Research Council. The result was the establishment of the Drug Efficacy Study (DES), in which panels of specialists evaluated the drugs used in their various disciplines. Two of the panels reviewed the cardiovascular drugs marketed between 1938 and 1962 which included approximately 300 products. The great majority of these preparations were antihypertensive agents of which the bulk were commercial products containing crude Rauwolfia serpentina or reserpine. Also included were diuretics, cardiotonics, peripheral vasodilator drugs, long-acting nitrites, miscellaneous agents, and a great variety of drug combinations. The experience gained in assessing this large number of pharmaceutical products seemed of sufficient general interest to warrant the present editorial.

Quality of the Evidence for Therapeutic Effectiveness

It soon became apparent after reviewing the pertinent literature that many claims of therapeutic effectiveness rested on flimsy evidence. Well-designed, controlled clinical trials were nonexistent in several categories of drugs. The supporting clinical data often consisted of nothing more than a few testimonials in which no attempt was made to control observer bias or the placebo effect. These deficiencies were particularly evident in the case of agents promoted for treating disease in which the principal measure of effectiveness was relief of a symptom, such as intermittent claudication or angina pectoris.

The problems inherent in assessing the effectiveness of a therapeutic agent on a variable and emotionally influenced symptom are well exemplified in the case of the long-acting nitrites administered orally. The frequency and severity of anginal attacks are far from constant from day to day, month to month, or season to season. Some of the practical problems that occur even in a well-designed therapeutic trial have been described by Cole and associates.[1] Only about one fourth of the patients referred for angina were judged acceptable for the trial. Some of those rejected had chest pain from other causes or had such conditions in addition to angina which made analysis of results impossible. Others were suffering primarily from anxiety and were unable to differentiate minor chest discomforts from true anginal attacks. Some patients were unable or unwilling to keep records of the daily incidence of attacks or number of nitroglycerin tablets used. Still others had attacks too infrequently to permit valid comparison of active drugs with placebo.

A revealing feature of this study was that half of the placebo-treated patients reported a decrease in the frequency of attacks continuing over the first 2 to 4 months of treatment. This illustrates the potent effects of the placebo and of the doctor-patient relationship on the manifestations of an illness such as angina pectoris. Indeed, none of the long-

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acting oral preparations evaluated in this study was more effective than a placebo.

Unfortunately, objective hemodynamic measurements have not been very helpful in defining the effectiveness of the coronary vasodilator drugs. Nitroglycerin dilates the large coronary arteries[2] but does not increase myocardial blood flow when given sublingually to patients with coronary artery disease.[3] The mechanism by which nitroglycerin relieves angina has not been entirely clarified. Reduction in arterial and left ventricular filling pressure appears to be equally as important, if not more important, than dilatation of the coronary arteries.[3, 4] In the absence of a clear definition of the hemodynamic mechanism of relief of anginal pain, it is not possible to use measurements of hemodynamic functions to assess the effectiveness of these drugs. Even the prevention or diminution of ST-T changes in the electrocardiogram during exercise by a coronary vasodilator drug[5] provides no assurance that the drug will be effective in the long-term prophylactic treatment of angina. Although the exercise electrocardiogram test may provide an additional index of effectiveness in a well-designed clinical trial, it cannot be regarded as a substitute for such a trial.

The panel was unable to find a conclusive therapeutic trial that documented the effectiveness of the long-acting nitrites administered chronically by the oral route of administration. In the absence of definitive evidence decisions had to be based on the available published reports and the clinical experience of the panel members. With regard to the peripheral vasodilator drugs evidence for therapeutic efficacy was even more deficient. Therapeutic claims often were based on nothing more than a few clinical reports, or rather testimonials, none of which bore any semblance of a controlled therapeutic trial.

Alkaloidal Mixtures and Drug Combinations

One of the panels reviewed the therapeutic claims of more than 50 marketed preparations containing either the crude root powder or partially extracted alkaloids of Rauwolfia serpentina. The marketing of such crude products is justified only if reliable methods exist for determining the constancy of the concentrations of the active alkaloids from one batch to another, and if the crude preparations are therapeutically equivalent to each other and to the pure active alkaloids. Such assumptions seemed questionable, to say the least, especially in the absence of methods for determining therapeutic blood levels of the active alkaloids. Any claims that the alkaloidal mixtures have greater therapeutic effectiveness or produce fewer toxic reactions than reserpine alone are not supported by the available clinical evidence. Thus, there seems to be no valid reason for continuing to place on the market a crude product of questionable consistency of action when active compounds are available as discrete chemical entities.

Some of the Rauwolfia combinations seem to be the result of wishful thinking, blind faith, and ignorance. Thus, there are combinations of Rauwolfia with mannitol hexanitrate and bioflavinoids, Rauwolfia with phenobarbital and theobromine, and even Rauwolfia plus vitamins. The problems concerning alkaloidal mixtures have been even further compounded by adding together the crude root powders of Rauwolfia and Veratrum.

The panels did not condemn all drug combinations. Although therapeutic agents should be added individually during the initial period of treatment so as to judge response to each drug, multiple agents are sometimes found to be more effective than a single drug. If the several effective agents are available in a single tablet approximating the doses found to be optimal during the initial therapeutic trial, substitution of the combination tablet then becomes desirable as a matter of convenience. In practice there are few such combinations. For example, an acceptable combination would be a benzothiadiazine diuretic and reserpine in appropriate doses for the treatment of chronic hypertension. Undesirable combinations would include mixtures of effective with ineffective agents, combinations in which one of the active constituents must be titrated over a relatively wide dose

range, and combinations in which one or more of the constitutents are present in inappropriate or ineffective doses as compared to the others. Unfortunately, the last is often the case.

Package Inserts

Package inserts or stuffers have been criticized previously as representing scraps of printed paper that are seldom seen by anyone other than the pharmacist. Although the criticism may be valid, the fact remains that at present the package insert represents the official and presumably authoritative statement transmitting pertinent drug information to the prescribing physician. It should, therefore, be accurate, objective, and consistent with current knowledge.

In actuality, however, the package inserts reviewed by this panel often fell short of the mark for which they were intended. Many were incomplete even to the listing of important precautions. For example, some digitalis inserts failed to indicate enhancement of toxicity produced by electrolyte imbalance, particularly hypokalemia secondary to administration of thiazide diuretics. In an insert on parenteral quinidine the need to monitor blood pressure during intravenous administration was not stated. Some of the small pharmaceutical companies marketing crude Rauwolfia provided only a few lines of information which were totally inadequate in all respects including data on side effects. In other instances, there was failure to indicate differences in therapeutic effectiveness using various routes of administration. For example, identical package inserts were used for the parenteral and oral forms of isoproterenol, no mention being made of irregular absorption after oral or buccal administration. These are but a few examples of important omissions.

Bias was frequently noted in subtle implications of superiority of one product over those of competitors. Some preparations were said to "more smoothly maintain blood levels" or to be "less irritating to the gastrointestinal tract." In neither instance was adequate documentation provided. One manufacturer claimed that its digitalis glycoside was similar to another in all of its therapeutic effects but was "better tolerated." Another indicated that their glycoside produced early warning gastrointestinal symptoms which lessened the danger of serious cardiac toxicity. No documentation could be found for either of these dangerously reassuring statements.

A related deficiency was the frequent tendency to state only the lower level of the effective dose range. This was particularly noteworthy with certain antihypertensive agents that are prone to produce side effects. The dose advised would not be effective in reducing blood pressure in many patients although it would minimize the incidence of side effects. The principal objective appeared to be to gain greater patient acceptability and use.

Many package inserts required updating. In the majority of the inserts relating to Rauwolfia serpentina and its alkaloids, the central nervous system was indicated as the principal site of action, no mention being made of the catecholamine-depleting effects of these drugs. Since catecholamine depletion by reserpine is by no means a recent discovery, it is apparent that these package inserts had not been revised for many years. Needless contraindications also were retained long after they had been refuted by adequate documentation. Many of the inserts relating to the nitrites and nitrates continued to cite glaucoma as a contraindication despite valid evidence to the contrary.[6] The majority of the Rauwolfia-reserpine inserts stressed the need to discontinue the medication 2 weeks prior to any procedure requiring generalized anesthesia. It is obvious that such delay may not be in the best interest of many patients, and, indeed, recent studies have indicated that it is unnecessary.[7]

Suggestions for Improvement

The examples of deficiencies in the package inserts just cited, while far from complete, should serve to indicate the need for a radical change in the official method of transmitting drug information to the prescribing physician.

The current proposal to replace package inserts with a national drug compendium written concisely and authoritatively by experts deserves support. The listing of all current drugs in a desk reference volume, providing it is accurate, up to date, and unbiased, will represent a real step forward in disseminating pertinent information on drugs to the practicing physician.

Many cardiovascular drugs need restudy using the technics of controlled clinical trials. Knowledge gained from a review of past deficiencies can be used in designing future, more definitive studies. In the case of the antianginal agents, for example, because of the limited numbers of acceptable patients the trial should be organized on a multiclinic basis. Precautions must be taken to provide a foolproof double-blind study, and the active agents should be given for a sufficient time to determine long-term effectiveness. The use of a pre-randomization trial period of several months' duration would allow a sufficient interval to establish a reasonably stable base line for the frequency of anginal attacks and also would serve to eliminate additional unreliable, uncooperative, or otherwise unsuitable patients. During this period the patients would continue to take nitroglycerin as needed but would also receive a placebo of a "long-acting" preparation. The post-randomization period could be interspersed with additional control periods as check points on the long-term fluctuations in the frequency and severity of anginal attacks.[1]

Report cards of the daily incidence of anginal attacks and number of nitroglycerin tablets required could be used in assessing therapeutic benefit. The exercise electrocardiogram taken both early and late in treatment with active drug or placebo would provide an additional criterion of effectiveness. Although such a study requires considerable planning and care in execution, it should provide definitive and urgently needed information.

In some other categories of cardiovascular drugs, documentation of therapeutic effectiveness was good or excellent. This was true in the case of the digitalis glycosides as well as with many antihypertensive agents and diuretics. Such examples serve to indicate that adequate assessment is possible when sufficient interest and support are given to the problem.

A well-conducted trial should indicate the frequency distribution of degrees of therapeutic effect in the population under study. It is far more informative to know the expected percentage of favorable responders to a given dose than to know, only in a general way, that a drug may be effective. To be complete such studies should include several dose levels of the drugs under study. In addition, an adequate clinical evaluation includes not only the percentage of patients achieving therapeutic effect in relation to dose but also the percentage showing toxicity relative to dosage.

Conclusion

The results of this review clearly indicated the need for more definitive information on the therapeutic efficacy of many cardiovascular drugs. These deficiencies should be corrected by instituting adequately designed, well-controlled detailed trials that are analyzed by appropriate statistical methods. In addition, more information is needed on absorption, distribution, metabolism, and excretion in man of commonly used cardiovascular drugs. In proceeding with this task we should remember Osler's admonition,[8] "This applies most particularly to treatment, in judging the value of which we should pray to be delivered from hasty judgments."

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