THE EVALUATION OF BETA BLOCKER AND CALCIUM ANTAGONIST DRUGS

edited by
J. Morganroth and E.N. Moore

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PREFACE

With the beginning of the 1980's it was becoming increasingly evident that the lack of approval of new cardiovascular agents for use by clinicians in the United States for the treatment of cardiovascular disorders was becoming a problem. Patients requiring medical therapy for hypertension, angina pectoris, arrhythmias, congestive heart failure, and vasospastic disorders of the coronary arteries could receive in the United States only a small number of the drugs available to physicians in the rest of the world. In fact, as the 1980's began, there was only one available beta blocking agent released by The Food and Drug Administration; and even as of this writing, no oral calcium antagonist agent. This lag, in part, has been due to the confusion of proper and expeditious methods to define safety and efficacy of such agents so that the United States regulatory agency (Food and Drug Administration) could approve the use of such agents by clinicians. The vast number of new beta blocker and calcium antagonist agents being developed, as well as the long-term use abroad of many new drugs, has raised important questions as to how relative safety and efficacy of such agents can be determined to facilitate availability in the United States.

The vast array of conditions in cardiovascular medicine that can be treated with either beta blockers or calcium antagonist drugs and the emerging evidence that such treatment cannot only markedly improve lifestyle by eliminating disease morbidity but also decrease the potential of developing sudden cardiac death emphasizes the importance to these classes of drugs.

The following manuscripts represent the collective efforts of physicians

and scientists from the United States and abroad as well as members of The Food and Drug Administration and the pharmaceutical industry to address this problem. The contributors have provided state-of-the-art papers which address the important topics in this field. Discussion sections, provided after each segment of the Symposium, allowed participants to express their viewpoints about the important issues and allowed consensus opinions to emerge. While we do not anticipate that this Symposium would evolve a unanimous consensus on means to expedite the proper evaluation of beta blocker and calcium antagonist agents, it was evident that it did identify important research questions yet to be answered and clarified many problems and points of differences between the various components participating in the Symposium.

We hope that this book will be useful as a reference for those individuals who design study protocols and define guidelines to determine the suitability of new beta blockers and calcium antagonist agents.

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INTRODUCTION

HOW TO EVALUATE NEW BETA BLOCKER AND CALCIUM ANTAGONIST DRUGS: THE CHALLENGE OF THE 1980s

Joel Morganroth, M.D.

In the 1970s it had become clear that overall cardiovascular mortality in the United States of America has been declining. Whether this improvement in longevity was due to alteration in the American diet, better detection of cardiovascular risk factors and their treatment, or to the more wide use of certain classes of new pharmacologic agents remained yet to be demonstrated.

The primary disorders in cardiovascular medicine which afflict the population include hypertension, coronary artery disease and electrical instability of the heart producing arrhythmias. About one dozen drugs account for about two-thirds of all prescriptions written by physicians in the United States for the treatment of cardiovascular disorders. This points to the relatively limited armamentarian available to clinicians in the United States compared to the scope of medical treatment available abroad.

One of the most important developments in the therapy of cardiovascular disorders was the availability of beta blocking agents because of their versatility, potency and relative safety. While beta blocking agents have important differences in terms of their membrane effects, intrinsic stimulating activity (agonist activity) and cardioselectivity, no data exists that one agent appears to be better than another for the treatment of cardiovascular disease. This class of agents can be used to treat patients with hypertension, coronary artery disease

and arrhythmias as well as other non-cardiovascular conditions. As of this writing, only three beta blockers have been approved in the United States; and these three agents account for over one-fifth of all cardiovascular prescriptions and approximately one-quarter of all new increased numbers of prescriptions so far in 1981.

Possibly the most significant advance in the last 20 years in cardiovascular medical therapy was the availability of beta adrenergic blocking agents. It is now felt that the most significant advance in the next 20 years will be in the evaluation and use of calcium antagonist blocking agents. Beta blocking agents provided an important insight into underlying physiologic mechanisms that regulate body systems in both normal and abnormal sates. While calcium antagonist agents have been used for many years outside the United States for the treatment of hypertension, coronary artery diseases and arrhythmias, none have been available for the treatment of patients in the United States until just recently.

The title of this Symposium is "How to Evaluate New Beta Blocker and Calcium Antagonist Drugs" and its purpose is to arrive at more precise and helpful guidelines to determine how to expedite the evaluation of efficacy and safety of these agents in order to hasten their release by the Food and Drug Administration.

This Symposium was organized by investigators and has no official sanction or political affiliations; and therefore, the comments herein expressed represent only those of the individuals involved. The funding of this Symposium was achieved by educational grants from over two dozen members of the pharmaceutical and related health care industries.

The organization of this Symposium was in two parts: Part 1 detailed the important issues in beta blocker agents. These issues included: #1--Whether there exists important clinically relevant differences between the various beta blocker agents; #2--What should be considered the recommendations on the most

expeditious means of defining efficacy of beta blocker agents as used in various clinical indications; #3--Comparative safety of beta blocker issues in general and in particular situations in which beta blocking agents are used with caution or are currently considered contraindicated; #4--Problems in study designs to answer these questions; and #5--The question of whether or not beta blockers prevent sudden death in patients post myocardial infarction.

Part 2 of the Symposium addressed the calcium antagonist agents. Topics included: #1--Whether there exists clinically relevant important differences between the various calcium antagonist agents; #2--How to expedite the definition of efficacy in various clinical indications and #3--Issues of safety and problems in the combined use of calcium antagonist and beta blocker agents.

The discussion sections following each of these segments of this Symposium were held to attempt to answer by consensus opinion the important questions raised. Active discussions between the academic investigators in the United States and abroad, scientists and advisors from the Food and Drug Administration and National Institutes of Health and representatives of the pharmaceutical and health care industry addressed these issues. It is our hope that this information can be used to establish new guidelines which will be used as the basis for an efficient and safe means of providing to the American public these new and important cardiovascular agents which we hope will be important contributions to the further decrement in cardiovascular morbidity and mortality.

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Beta-Adrenoceptor Blocking Agents: Historical Perspectives

William B. Abrams, M.D.

Introduction

The availability of beta-adrenoceptor blocking agents has been recognized as a major therapeutic advance of this century. They have proven effective in the control of certain cardiac arrhythmias, provided the first effective therapy for the chronic management of common angina pectoris, contributed importantly to the control of high blood pressure, provided well-tolerated topical treatment for glaucoma and are clearly useful in the management of IHSS, migraine headaches and other disorders. Even more important, evidence is accumulating that beta-blockers preserve life when used acutely and chronically in patients suffering myocardial infarction. It is self-evident that many of the disease states for which beta-blockers have been found effective are serious, disabling, and/or life-threatening. This speaks for their importance in our therapeutic armamentarium. How did they come to be? Their history will be traced through their basic science, therapeutic and regulatory tracks.

Basic Science

Since there is no substantial evidence that these drugs act by a mechanism other than the blockade of beta-adrenergic receptors, the story begins with the understanding of the pharmacology of the sympathetic nervous system. In 1905, Langley suggested that neuromuscular cells contained both excitatory and inhibitory receptors in

explaining the actions of epinephrine.[1] A year later, Dale reported the antagonism of ergot derivatives for the excitatory, but not the inhibitory vascular actions of epinephrine -- except for the heart![2] On the basis of these observations, he proposed the existence of at least two types of receptors, one of which could be blocked by ergot.[2] The concept was temporarily sidetracked by Cannon and Rosenbleuth who proposed the presence of dual neurohumoral mediators: Sympathin I and Sympathin E.[3] However, in 1946 Van Euler demonstrated that norepinephrine was the single adrenergic neurohumoral transmitter substance.[4] Two years later, Ahlquist classified adrenergic receptors as alpha or beta according to the rank orders of potency of six sympathomimetic amines in several physiologic systems.[5] His concept was confirmed a decade later when Powell and Slater synthesized dichloroisoproterenol and observed its blocking effects on activities now known to be beta-mediated.[6] DCI was not useful therapeutically because of its potent intrinsic sympathomimetic activity. The first clinically useful beta-adrenoceptor blocking agents were pronethalol and propranolol, synthesized by Black and Stephenson.[7,8] Pronethalol was dropped early because of tumorigenic actions in animals. As research expanded it became clear that more than one beta-receptor existed[9] and this was confirmed pharmacologically by Furchgott in 1967[10] and clinically when the cardioselective beta-blocker practolol was introduced.[11] Studies in animals and man made it clear that beta-adrenoceptor blocking agents could be classified according to certain pharmacologic activities in addition to the common property of beta-blockade. By the end of the 1960s, the beta-mediated sympathetic functions were well-defined and numerous beta-blocking agents were in use or under investigation.

Therapeutics

The potentially adverse effects of catecholamines and inappropriate sympathetic nervous system activity on the heart and circulation were well-known when the beta-blockers arrived on the scene. It is not surprising, therefore, that their use in cardiac arrhythmias, angina pectoris and hypertension was studied early.[12] It is surprising, however, that the cardioprotective effect in myocardial infarction was also studied early,[13] although it took 15 more years to convincingly prove the value.

Cardiac Arrhythmias

A year after the initial publication on pronethalol appeared, Stock and Dale reported on its effects in various cardiac arrhythmias.[14] Their principal finding was that this beta-blocker was useful in slowing the ventricular rate in atrial fibrillation. They also noted utility in suppressing digitalis-induced ectopic beats and tachycardias. On the adverse side, they observed the drug could precipitate or aggravate heart failure when used in this setting. Although much clinical and laboratory research has followed, not much of clinical relevance has changed. Atrial tachyarrhythmias other than fibrillation are considered indications as are arrhythmias associated with sympathetic over-activity.[16] Therapy is more effective because of knowledge gained by pharmacokinetic studies.[17] Propranolol, approved for this purpose in 1967, is the only beta-blocker available for use in arrhythmias in the United States.

Angina Pectoris

As early as 1948, Raab called attention to the potentially deleterious effects of cardiac sympathetic activity in patients with angina