Cardiovascular Drug Development

Protocol Design and Methodology

edited by
Jeffrey S. Borer
John C. Somberg

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In memory of Howard Gilman,
who sheltered the weak, supported the struggling,
and embraced the vulnerable

Introduction

As Editor-in-Chief of the ''Fundamental and Clinical Cardiology'' series, it is with tremendous pride and appreciation that I introduce this superb book by Drs. Jeffrey Borer and John Somberg. The new millennium is an especially exciting time to practice cardiology because of the exponential discoveries and implementation of cardiovascular drug development. Drs. Borer and Somberg have highlighted five critically important areas for general cardiovascular practitioners: congestive heart failure, hypertension, arrhythmia, hyperlipidemia, and coronary artery disease. Not only do they present didactic expositions but, importantly, they moderate controversial panel discussions. Having trained with John Somberg at the Peter Bent Brigham Hospital, I find it a personal pleasure to welcome the publication of *Cardiovascular Drug Development.*

Samuel Z. Goldhaber

Preface

During the past 25 years, the progress of cardiovascular drug development has dwarfed all previous efforts in the area and has led to important benefits for public health. Nonetheless, cardiovascular drugs generally allow only a relatively small margin between useful efficacy and acceptable safety when used for treatment of the major cardiovascular diseases. As a result, development of therapeutic agents in this field presents unique challenges. These challenges have been complicated as the discovery of life-prolonging benefits of some regimens has mandated background therapy to which new drugs must be added. The attendant risk of deleterious drug interactions has importantly circumscribed the list of molecules that can be developed. Also, as therapeutic options have increased, standards of evidence for addition of new treatments have become increasingly rigorous, with concomitant and dramatic increases in development costs. The need for cost minimization and efficiency in drug development has generated multinational efforts to find appropriate study populations and other necessary resources. As a result, today molecular discovery, preclinical development, and pivotal clinical studies for drug approval routinely are performed on an international basis. These changes in the patterns of drug development reflect parallel changes in the previously insular pattern of biomedical research and, in turn, have led to considerable efforts to ''harmonize'' drug regulatory principles among the regulatory agencies of the United States, Europe, and Asia.

Eighteen years ago, John Somberg organized the first of what became an annual series of symposia entitled, ''Advances in Cardiovascular Pharmacology: Protocol Design and Methodology,'' held in

Washington, D.C. The purpose of this effort was to bring together members of the regulatory, academic, and pharmaceutical development communities to discuss cardiovascular drug development. The annually recurring program consists of ''mini symposia'' on the development of antihypertensive agents, antiarrhythmic drugs, drugs for congestive heart failure, antianginal/anti-ischemic drugs, and antithrombotic, thrombolytic, and lipid-lowering as well as other antiatherosclerosis therapies. All these areas have undergone radical changes over the last two decades, in both molecular development and regulatory standards. However, application of the symposium format to review and consider this evolutionary process has proven enduring and useful.

Recognizing the international trends, Dr. Jeffrey Borer joined with Dr. Somberg in 1990 to extend the symposia beyond the United States to encompass the views and concerns of the international drug development communities. The result has been an annual companion series in which differences in approval standards and approaches to drug development among different nations are discussed. Three years later, portions of the United States and international symposia first were published. With the present publication, the long-planned goal of disseminating a volume of proceedings that touches upon all areas of cardiovascular drug development has finally been achieved.

This book includes material from both the spring (U.S.) and autumn (international) symposia of 1996 to 1997. The format of the symposia is composed of brief formal presentations followed by extended panel discussions. The publication presents the formal discussions, edited for clarity, followed by transcripts of the panel discussion, edited by Drs. Borer and Somberg. Each drug development area is introduced with a brief overview discussion of the state of the field, highlighting areas of controversy as well as accepted approaches to amassing the database necessary for drug approval by regulatory agencies, most particularly by the U.S. Food and Drug Administration. No effort has been made to be encyclopedic in discussing drug development trends in any single symposium, nor is this volume intended to provide such comprehensive coverage of the field. Expansion of this format is anticipated in future editions, which will result in such a comprehensive primer.

We hope that this volume will prove useful for those who have

not been able to attend the symposia, as well as for those who wish to review and revisit materials covered in past meetings. Cardiovascular drug development is an important field because of the debilitating and potentially lethal nature of cardiovascular diseases and because of the high prevalence of these conditions in our society. The impact of medical therapeutics has been considerable and accounts for substantial reductions in cardiovascular morbidity and mortality. We hope the spring and autumn symposia, as well as this book, will contribute in some way to furthering development of these important therapies.

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Drug Discovery and Development

John C. Somberg

Change is part of the human condition that we often fail to notice. Over the last 100 years, the drug development process has undergone considerable, perhaps even revolutionary, change. But perhaps all that has passed will pale in comparison in the dramatic new information era, which will markedly alter the environment we work in and the drug development process.

Even the most powerful and financially stable companies engaged in drug discovery and development need to recognize the forces of change. The evolution of the computing age gave IBM the opportunity to expand and alter its business from analog systems and adding machines to punch cards and then to complex computer systems. As the computer age developed, IBM led the way with the innovative personal computer. The lead was then lost by IBM when ''software'' became the core of the information age, along with the chips that permit the exponential growth in machine computing performance. Thus, Microsoft, just a concept 20 years ago, is more dominant in today's information age than IBM. IBM remains a leader in technology advances, in new fundamental patents, and in strength of marketing and sales force. It kept up in technology, but its management failed to perceive the salient change in the information age from large computers to small, and then to the importance of the operation language that controls information processing, analysis, and communication.

Drug development is in an analogous situation. We have seen an

evolution from the age of botanicals to the age of chemical synthetic discovery and now to the age of biotechnology and gene manipulation, which is dawning today. Each area can still grow, but the shift in direction is fundamental to scientific development. Taking these major changes into account, drug discovery and development will be fundamentally altered by the information age. The concept of the information age had been coined by Toffler and was correctly perceived to be revolutionary in its effects on society. The agricultural and the industrial revolutions brought about fundamental changes in society, as will the information age. In his book entitled *Future Shock* (1), Toffler describes an era when the pace of change in modern life is so great as to disenfranchise individuals from the process that society is undergoing. While this is a real problem for society and a problem with political dimensions, failure of our institutions and of our corporate structures to adjust will bring considerable societal and economic disruption. For these reasons, an understanding of the evolution of drug discovery and development and how this evolution will be affected by the information age is essential for those working in this area.

THE AGE OF BOTANICALS

Anthropologists tell us that even in the early times of hunters and gatherers, humans made use of herbals. Whether as foods, items of religious significance, or medication cannot be clearly discerned. As civilization progressed, remedies from plants further developed. Earliest folklore relates stories of plant medicinals. The bible contains passages eluding to medicinal herbs and plants. In fact, all the major religions discuss plant remedies as part of their sacred works. There are many stories in pharmacology relating to the use of medicinal plants and the work of herbalists in the early discovery of drugs. I recall the story of William Withering, the physician from Birmingham, England, who on his charity rounds in Shropshire saw that an herbal potion was used to treat a woman with dropsy (CHF) who then showed improvement. Withering's botanical training in Edinburgh permitted him to identify the probable active ingredient, the leaf of the foxglove plant. After 10 years of clinical experimentation, he developed a series of case studies ex-

plaining the dose range from minimal effective dose to toxicity. He categorized the adverse side-effect profile of the digitalis leaf and its potentially life-threatening toxicities. He noted the adverse outcomes and carefully chronicled the conditions that the drug was most useful in treating. While he thought the agent increased urine volume and, thus, had diuretic properties, he commented in his thesis that the drug had a powerful action on the motion of the heart and, thus, recognized its cardiotonic action years before this was actually proven. Withering was a masterful botanist (he chronicled the plants of Great Britain later in his life). He was an exemplary clinical pharmacologist and demonstrated the best in botanical drug discovery and testing given the skills of his day. But Withering's observations may not be unique. The effect of the foxglove plant on disease was known to be part of European plant folklore. The use of these glycoside-yielding plants and the use of the skin of the toad for medicinal purposes goes back to ancient Egypt, and is also mentioned in Chinese herbal writings. Confucius talks of glycoside plants for edematous states and cardiac glycosides are a significant component of Chinese herbal medications. While Withering's observations were a defining moment for modern medicine, botanicals of similar action were used for over 2000 years. Clearly, botanicals have been an important component to therapeutic advances. Whether we are discussing digitalis or atropine or any number of other drugs, plants have contributed much to drug discovery. The use of quinidine in atrial fibrillation or quinine to treat malaria are other examples of the importance botanicals have played in therapeutics. In fact, in the 1700s and 1800s, botanicals were the only source of drugs for development. The anti-infective agents have depended on extracts from molds and fungus for a very long time. Recent therapies are derived from nature with some chemical modifications to improve activity. We often think of the age of botanicals as one that has gone by. Indeed, it was the first step in the field of drug discovery and development, but one that continues to this day to play a major role. While reserpine was used for a thousand years in India and parts of China, it was only in the 1950s that it was purified and used as an effective antihypertensive agent. The recent use of taxol in oncology is an example of a botanical that was in very short supply. Until a synthetic pathway for commercial production was developed, the bark of the hew

tree became a very valuable commodity and caused the hew tree to be endangered. In fact, some companies like Schaman Pharmaceuticals have made it their corporate purpose to discover and develop pharmaceuticals from botanical sources. We read about Merck & Company and Pfizer, to name but a few of the corporate giants, who have formed special alliances with botanical gardens, countries in South America or Africa, or both, to find new drug products. Is this a denial of the evolution of drug discovery, a last chance for the botanical pioneers, or a shrewd business decision? I would venture to say a bit of each. The biodiversity of the planet, the potential to find new antibacterials and other potentially useful pharmaceuticals is great. However, the need to assay so many compounds for a host of disease states and the imperfect capacity of our assays makes the odds of success much less likely than one might first estimate. Another critical aspect to the drug development process from botanicals is the fallacy of uniqueness. By this I mean the assumption that nature will provide a unique agent that can be purified and have a salutary action on a disease state with little to no organ toxicity. These assumptions are naïve and may not be correct. However, the biodiversity may provide chemical structures that can be modified or redesigned, which can be useful starting points for the drug discovery process. However, we must be smart enough to use the information we collect. Techniques are going to be needed for the categorization and analysis of what the botanical explorers find.

Another aspect is that once we find a useful agent, can we utilize today's technology to amplify its utility and insure its availability in industrial quantities. These considerations are most important to industry. Supplies of plant pharmaceuticals can be very limited. We need to employ the technologies of recombinant DNA biotechnology to provide for commercially available quantities of many of these botanicals that may be discovered. It may be that the chemical synthetic process is cheaper and this also must be considered as an alternative supply route once the novelty of the compound and its utility at clinical practice has been established. There are indeed drugs that can potentially be obtained through botanical sources. However, a systematic program is going to be needed to develop possible leads, explore them, and then to provide for adequate quantities of the substance.

The evolutionary process has created a great biodiversity. This

does offer great potential, but we must realize that there is a limited window of opportunity to make use of this opportunity. Humans have unfortunately negatively impacted on the environment and perhaps this adverse impact of the industrialization of the world is unavoidable. However, this diversity does offer tremendous possibilities for drug discovery, but as the diversity is impacted upon and diminished, the potential for discovery is also diminished. Utilizing this diversity is a challenge, one that has been assumed by a number of recently devised projects. To successfully deal with the challenge requires the application of the most modern techniques, the most important of which may well be those related to handling the vast amount of information that can be collected. Clearly, computer applications to the exploration of the plant world, its categorization, automated process for analysis, and chemical categorization with innovative storage, organization, and retrieval will be required to make the drug discovery process effective. The systematic computerization of knowledge in ethnobotany and pharmacognosy, with emphasis on plant categorization across primitive societies, will be helpful to sustain the discovery process. Using sophisticated computer techniques to look for similarities in medicinal plant use among primitive peoples to ascertain potentially useful observations can greatly aid the ethnobotanist. Hopefully, these computerized techniques will replace the hundreds, if not thousands, of years that are needed for serendipitous observations such as that made by William Withering 200 years ago, which led to the introduction of the digitalis glycosides in clinical medicine.

CHEMICAL SYNTHETIC DISCOVERY

Over the last 75 years, the majority of new molecules have come from synthetic chemistry. In cardiology, the beta blockers and calcium channel blockers have revolutionized cardiovascular therapeutics. Beta agonists in respiratory therapy and H_2 antagonists in gastrointestinal ulcer disease therapy are a few examples of the work of the synthetic chemist that has greatly changed our treatment of patients. These advances represent all that is created in synthetic chemistry, as well as the proven model of finding a useful transmitter in a physiological system, finding