Editorial

What Have We Learned From the Calcium Channel Blocker Controversy?

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Hundreds of thousands of patients around the world have been treated with drugs that antagonize the function of calcium channels. The development of these drugs was based on the remarkable scientific discovery of calcium channels, the identification of methods to antagonize their effects, and the development of compounds to block them.\textsuperscript{1,2} As concepts of the pathophysiology and treatment of hypertension and atherosclerosis evolved in parallel with the science of calcium channels, an approach to determining whether these therapies have clinical benefit was developed.

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In the treatment of hypertension, the strategy for therapeutic evaluation has been based on the simple concept that lowering blood pressure will result in a decrease in the incidence of stroke, myocardial infarction, renal failure, and death.\textsuperscript{3} In the treatment of angina, a more complex set of concepts has prevailed. Three factors have formed the framework for evaluating therapies for angina: (1) the role of coronary vasospasm in the production of myocardial ischemia,\textsuperscript{4} (2) the belief that reduction in myocardial ischemia over a specified time interval or improvement in exercise time on a treadmill provided strong evidence of an overall health benefit,\textsuperscript{5} and (3) more difficult extrapolations related to preservation of cellular function during myocardial ischemia.\textsuperscript{6} The synthesis of these factors has led to the acceptance of a reduction in frequency of angina or an improvement in exercise time as adequate evidence of a desirable clinical benefit of a therapy for angina.

On the basis of these constructs, a variety of compounds were developed that had disparate properties but the common action of antagonizing calcium channels. Regulatory authorities in the United States and other countries approved these agents for clinical use on the basis of their pathophysiological constructs, relying on evidence that they lowered blood pressure or improved exercise time. Hundreds of small, carefully conducted, randomized trials of these compounds have been completed, but many of them (especially those with negative results)\textsuperscript{7} have never been reported in the medical literature. The vast majority of these studies evaluated uncomplicated patients who could reasonably be expected to complete the trial without clinical events or poor outcomes related to comorbidity. When released for clinical use, the drugs contained careful labeling restricting them to the populations and indications for which they had been shown to be effective. Aided by the opinions of influential thought leaders,\textsuperscript{8} clinicians have attempted to extrapolate the findings of these small, carefully controlled studies to more general populations, including patients with complex, high-risk coronary disease and multiple comorbidities.

Only after the early calcium channel blocking agents had been marketed for some time did an initial warning signal come from several publications. An association was reported between short-acting nifedipine and an increased incidence of adverse myocardial ischemic events;\textsuperscript{9} this concern was reinforced by regulatory authorities.\textsuperscript{9} A systematic overview of postinfarction therapies echoed their concern.\textsuperscript{9} Several studies subsequently demonstrated that these agents carried significant risk in patients with left ventricular dysfunction.\textsuperscript{10,11} Despite these publications, short-acting nifedipine continued to be widely prescribed, other calcium channel blockers were broadly used in patients with left ventricular dysfunction, and no action was taken to restrict them. Then, after a hiatus, a case-control study\textsuperscript{12} raised the possibility that calcium channel blockers could result in substantial mortality and morbidity in a general population with hypertension, especially in contrast to other logical therapeutic choices. Since then, a substantial public controversy has erupted,\textsuperscript{13,14} raising questions about medical practice, science, business, and the role of government in the regulation of therapies for chronic, life-threatening illnesses. Many interesting questions have arisen about whether all these agents produce the same clinical outcomes and the mechanisms by which their effects on clinical outcomes differ. A critical question with implications far beyond the specific use of calcium channel blockers is why well-intentioned physicians continue to prescribe a class of drug to thousands of patients every year in the absence of a clear understanding of their effects on the health of the patients for whom they are prescribed.

The most recent study, by Michels and colleagues,\textsuperscript{15} in conjunction with other recent publications,\textsuperscript{16} points out the complexity of the evidence that we must consider before deciding whether calcium channel blockers as a class, or any individual calcium channel blocker, are deleterious or beneficial to the overall health of patients. In 14 617 nurses participating in the Nurses’ Health Study who had a diagnosis of hypertension, those taking calcium channel blockers had higher rates of death and myocardial infarction than nurses prescribed another class of drug. However, the group of nurses on calcium channel blockers were also more likely to...
have diagnosed coronary disease, diabetes, prior myocardial infarction, and prior stroke.

It is fascinating to note that in such a highly educated patient population, nurses with a higher risk of cardiovascular events had a higher rate of use of calcium channel blockers than nurses with a lower risk, despite extensive coverage of the controversy in the medical literature. This finding of more calcium channel blocker use in higher-risk nurses makes interpretation of the worse outcomes in the nurses who were treated with calcium channel blockers difficult. The authors appropriately conclude that investigators are unlikely to resolve the question of whether short-acting calcium channel blockers have deleterious effects with observational studies, despite their many years of use in clinical practice, and that only with ongoing direct comparative studies will the impact of these agents on important clinical outcomes be determined.

This study raises the important question of why we have definitive clinical outcome information about therapies in some conditions, such as acute myocardial infarction, whereas we have almost no such information about the overall health effects of most commonly used therapies. Definitive information about the mortality effects of ACE inhibitors and β-blockers guides the clinician in the treatment of ischemic heart disease, yet there is no reasonable long-term information on medical outcomes from adequate randomized trials about the treatment of type II diabetes, obesity, asthma, depression, or comparative therapies for hypertension. In each of these conditions, significant damage could be done by commonly used therapies prescribed by well-intentioned physicians. The clinical benefit of effective therapies, on the other hand, may be minimized by a lack of adequate outcome data to present a compelling need for treatment.

Whose responsibility is it to ensure that appropriate studies are done? We believe that when physicians and other healthcare providers take the lead in pointing out the need for adequate outcome data and in providing the mechanisms to obtain these data, as the ISIS investigators did with acute myocardial infarction treatment, the other constituents will collaborate to obtain the desired information.

An examination of the roles of the major participants in clinical research provides considerable insight into the reasons for significant progress toward knowledge of outcomes in some areas but not others. Clinical research involving human experimentation has designated roles for healthcare providers, regulatory authorities, and a sponsor, usually either the government or the medical products industry. In some situations it is considered the norm to conduct clinical trials designed to determine the impact of the treatment on clinical outcomes, including death and adverse events such as stroke and heart failure. In other situations, such as the evaluation of calcium channel blockers in the treatment of hypertension and angina, clinical investigation has stopped with the measurement of pathophysiological surrogates (blood pressure) or clinical measurements that reflect a short-term outcome (exercise treadmill time).

When the regulatory process does not demand true clinical outcome information before a therapy is marketed, two common misconceptions ensue. The first is that government funding will be available through the National Institutes of Health or the Agency for Health Care Policy and Research to ensure that the therapy is beneficial. The second is that physicians and patients will be able to discern that a treatment is detrimental from their experience with its use in their personal practices. Unfortunately, however, the government is unable to support the amount of clinical research that needs to be done to determine which therapies are beneficial and which are detrimental. And, as we have learned the hard way, prophylactic therapies in cardiovascular disease cannot be assessed by the impressions of individual practitioners. Even if an adequate sample size existed in an individual practitioner’s office, and usually it does not, the complexity of chronic disease outcomes makes it very unlikely that a modest but clinically very important increase in mortality would be discernible. The recent “fen-phen” diet drug problem is an excellent example of the failure to detect a deleterious effect before marketing. The harm was initially detected by astute observers because of the severity of the defect it caused, but only after thousands of patients had been treated.

The medical products industry is appropriately concerned with making a profit to report to its shareholders. This capitalistic approach produces considerable reward for creative endeavor and should be continued. If regulatory groups do not require long-term clinical outcome data in the broad population of patients in whom the treatment is likely to be used, industry is faced with a choice between performing definitive and expensive clinical outcome studies and doing less expensive, small, complicated studies addressing surrogates or mechanisms. The clinical outcome study, such as a mortality trial or a stroke prevention study, is attractive when it is positive, but a negative trial creates a significant commercial risk. By comparison, a series of small studies aimed at pathophysiology, coupled with support of small research and educational programs by academic leaders, creates a less definitive, less expensive, and less risky approach to product development. These inadequate studies leave the academic community suspect when leaders advocate one therapy or another without definitive clinical outcome support.

Why would regulatory authorities not demand definitive evidence about whether a drug increases the risk of mortality or stroke when prescribed for hypertension and angina? Regulatory authorities meet historical standards, set by legislative bodies, for determining safety and efficacy, and they are charged with labeling therapies for the context in which they were studied. Most calcium channel blockers are labeled to lower blood pressure in patients with hypertension or to improve exercise tolerance in patients with angina. If they were not studied in a trial large enough to produce reliable estimates about their effect on mortality, they cannot be labeled to indicate whether a mortality effect, positive or negative, is present. The fact that this labeling leaves open the question of how to use the therapies in the millions of patients with angina or hypertension and left ventricular dysfunction or another comorbid condition represents a flaw in the interface between the regulatory system and the practice of medicine.

Perhaps this gap would be much smaller if physicians and other healthcare providers became more knowledgeable about these issues with regard to therapies that are commonly prescribed. Our willingness to accept short-term measures of outcome in narrowly focused patient populations and to
broadly extrapolate them to much more diverse patient populations has created a situation in which most of the therapies for chronic diseases have never been assessed for their overall health outcomes. Until the past decade, the concept of large outcome studies would have been considered a dream. The advent of global communication through computers and the development of large, simple trial methodology have provided a realistic possibility for adequate studies by allowing the rapid enrollment of patients around the world to achieve adequate sample sizes to assess clinical outcomes.

The remaining impediments to the implementation of adequate clinical trials measuring outcomes fall into two categories: cultural and financial. Until recently, clinical investigation was regarded as an endeavor for specialists in academic settings, and the concept of randomizing patients in practice seemed unreasonable. The ISIS investigators and others have demonstrated both the desirability and the feasibility of changing this culture. Practitioners gain a different perspective when they recognize that prescribing a therapy in the absence of knowledge about its potential for benefit or harm is an irresponsible experiment compared with encouraging a patient to participate in a randomized trial that will provide that information. If practitioners incorporated clinical research into their clinical practices in hopes of creating a system to constantly improve the understanding of therapies and the diseases they were designed to treat, the cost of doing clinical trials would diminish, and both patients and practitioners would be much better off. The continuing acceptance of common nomenclature and clinical information systems provides a mechanism to dramatically reduce the cost of trials. Such an approach would have the further benefit of identifying therapies that could be discarded for lack of effectiveness, leaving more funding for therapies that are truly beneficial to patients.

Patients expect their doctors to know whether the therapy they recommend will be helpful or harmful. Doctors can no longer claim that the methodology to determine the overall health effects of a given therapy is not feasible. Large, randomized trials assessing therapies for common chronic diseases such as hypertension need to happen sooner rather than later in the development of new therapies, and these same types of trials are needed to identify the older therapies that are truly beneficial. Fortunately, several such trials are now ongoing in the field of hypertension. Given our current knowledge of the fallacy of surrogate outcome measures and the difficulty of interpreting confounded observational analyses, it is imperative for practitioners to become producers of the evidence for evidence-based medicine and not just consumers of the evidence. In this modern era, in which the possibilities for medical care exceed society’s willingness to pay, it is vital to the interest of our patients that we admit that gaining definitive knowledge about the therapies we prescribe is our professional responsibility. Until we shoulder that responsibility, our patients will suffer needlessly from damage done by the overuse of detrimental but inadequately understood therapies and the underuse of beneficial but inadequately understood therapies. In the case of calcium channel blockers, many years and thousands of patients later we still do not know which problem, overuse or underuse, we have created.

References


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