Although it is widely accepted from experimental studies that timely reperfusion limits myocardial infarct size, reperfusion by itself may not achieve the greatest possible effect. In a clinical setting, reperfusion, whether by thrombolytic therapy or emergency coronary angioplasty, never can be achieved instantaneously. Thus, adjunctive therapy, which could either slow ischemic metabolism and cellular injury pending successful reperfusion or protect myocytes against undesired, potentially lethal effects of reperfusion (“lethal reperfusion injury”), should have added clinical benefit for limiting infarct size. Moreover, it would be possible to treat patients at high risk of infarction prophylactically if a safe and effective cardioprotective agent could be developed.

Several endogenous mechanisms or exogenous interventions are known to both slow the rate of ischemic metabolism and delay the onset of lethal myocyte injury. For example, the speed at which ischemic cell injury occurs is markedly temperature-dependent. Hypothermia substantially slows ischemic metabolism and the onset of lethal myocyte injury.\(^1\) This approach is commonly used in cardiac surgical procedures requiring a cessation of myocardial blood flow to slow ischemic injury and thereby prolong the tolerable period of ischemia.

Studies in several animal species have shown that exposing myocardium to \(\geq 1\) short (5- to 15-minute) episodes of ischemia (“ischemic preconditioning”) slows energy metabolism and delays the onset of myocardial necrosis in a subsequent prolonged period of ischemia.\(^2,3\) Although the mechanism is not completely established, there is considerable evidence that the effect requires activation of \(\geq 1\) signaling pathways, the end effect of which is enhanced opening of ATP-dependent potassium (\(K_{\text{ATP}}\)) channels.\(^3\)

Calcium channel blockers also generally have had cardioprotective, infarct-limiting effects in studies based on an animal model in which infarcts were induced by relatively short periods of ischemia (40 to 90 minutes) followed by reperfusion.\(^4,6\) Thus, calcium antagonists delay but do not prevent lethal ischemic injury in experimental models.

Calcium channel antagonists are now frequently used in the treatment of clinical myocardial ischemia (angina pectoris). However, assessment of their clinical benefit has been controversial, and the value of calcium antagonists in patients with acute myocardial infarction is even less clear. Earlier clinical trials testing the effect of calcium antagonists, including verapamil, diltiazem, and nifedipine, in the setting of acute myocardial infarction failed to demonstrate a beneficial effect on patient survival.\(^7-9\) One hypothesized reason for the lack of overall clinical benefit of calcium antagonists has been that the classic agents have substantial negative inotropic effects, a serious drawback especially when myocardial function may already be depressed by the evolving myocardial infarct.\(^10,11\) Because of these drawbacks of earlier calcium antagonists, a calcium antagonist with little or no intrinsic negative inotropic activity could be an attractive alternative for clinical application if it showed equivalent infarct-limiting efficacy in experimental models.

Mibebradil (Ro 40-5967) is a calcium channel antagonist that, in experimental animals\(^12,13\) as well as clinical studies (involving patients with angina pectoris),\(^14\) was found to lack the substantial negative inotropic effect of verapamil. This attribute suggested that mibebradil might offer unique advantages over previous calcium channel blockers in clinical ischemic heart disease. An initial study of short-term ischemia and reperfusion in dogs showed that mibebradil limited myocardial infarct size to a degree similar to that achieved by verapamil in the same study.\(^15\) Mibebradil also was reported to limit myocardial infarct size in rats.\(^16\)

In the present issue of Circulation, Schulz et al\(^17\) report the results of a comparison of the effects of 3 calcium antagonists on myocardial infarct size in pigs. These authors observed that mibebradil limited infarct size independently of any hemodynamic effect, whereas amlodipine did not limit infarct size. Verapamil limited infarct size, but its effect was abolished when the associated hemodynamic effects of verapamil were eliminated. In addition, Schulz et al report that the infarct-limiting effect of mibebradil was abolished by blockade of \(K_{\text{ATP}}\) channels, which raises the possibility of a common mechanism between mibebradil and ischemic preconditioning.

Despite the promise of molecules such as mibebradil based on animal studies, clinical efficacy must be proven through clinical trials and safety must be validated through postmarketing surveillance. The standard for clinical efficacy is prolongation of life, reduction in symptoms, or prevention of major events in patient groups representing the population of intended use. To evaluate one of these end points without...
considering the others would be a mistake. Incorrect therapeutic application has occurred in several previous drugs because of insufficient information on all of these aspects from the relevant population of patients. In the specific case of mibebradil, an unfortunate series of events has led to its withdrawal from the market and consequent elimination of its promising experimental efficacy in limiting infarct size.

In a series of elegant and carefully controlled phase I, II, and III clinical trials, mibebradil was developed as a therapy to reduce angina and treat hypertension. The angina trials recruited patients without complex comorbidities. Using serial treadmill exercise testing, patients given mibebradil were able to exercise longer than patients given placebo. Mibebradil-treated patients also had fewer episodes of angina. The hypertension trials recruited patients with simple essential hypertension and proved that mibebradil can lower blood pressure and that its antihypertensive efficacy was comparable to or better than that of other currently available therapies. “Hard” clinical events such as death, myocardial infarction, or new-onset heart failure occurred at a very low rate in these studies because of the low-risk nature of the population and the short duration of the studies. The drug was noted to cause an abnormality of the QT interval; debate ensued over whether this abnormality represented true QT prolongation or simply a normal QT variant. Comparison with other calcium channel blocking agents showed similar QT effects of diltiazem and verapamil. Only 1 small study was completed in patients with heart failure at the time FDA approval was sought, and a nonsignificant excess of deaths was seen in mibebradil- versus placebo-treated patients.

The company proposing to market mibebradil, to its credit, had commissioned a properly designed mortality trial in heart failure (MACH-1) that was adequately sized to detect a major negative impact of the compound, but at the time of application for marketing, the results of this trial were not available. Pharmacokinetic studies had demonstrated that the P450 enzyme system was involved in its metabolism, and interaction studies had demonstrated a substantial increase in concentrations of both mibebradil and at least 1 statin when both were given to human subjects.

On the basis of the above information, the Cardiorenal Panel of the FDA recommended approval of mibebradil for marketing, and the agent was marketed in June 1997. Clinicians were advised to use caution when combining mibebradil with other compounds metabolized by the P450 system. Within 4 months, >400 000 patients were taking mibebradil for either hypertension or angina.

Shortly after marketing, however, reports began to surface of toxicity, including torsades de pointes, clearly related to interactions between mibebradil and other therapeutic drugs. Apparently, no significant toxicity could be attributed to mibebradil alone; it always occurred in conjunction with another major complicating factor, almost always another potential culprit drug. The MACH-1 trial unfortunately found a nonsignificant trend toward a higher mortality with mibebradil than placebo (27% versus 24.6%). The adverse outcome reports became numerous despite major efforts to better educate physicians about the potential for drug interactions. The MACH-1 trial also failed to eliminate the adverse events.

The result was the removal of the agent from the market. It is no longer available for clinical use.

How could a drug with so many positive properties and with so many well-done clinical trials have gotten onto the market and been used by so many patients before it met its terminal fate? We believe that review of the outcome of the development of mibebradil provides convincing evidence that chemical entities (and devices) must be evaluated in trials that assess total health outcomes in patient groups reflecting the population of intended use. Settling for surrogate end points, such as physiological parameters, and small trials of low-risk populations studied for a short duration will expose our patients to substantial risk of unintended adverse consequences.

A systemically administered drug almost always has a combination of desirable effects and undesirable effects, at least some of which cannot be anticipated until the drug has been studied in patients with the diseases being treated who have relevant comorbidities commonly seen with the target diseases. In an increasingly complex clinical environment, in which a greater proportion of patients are older and often have multiple comorbid conditions, “proof-of-principle” studies in small populations provide an excellent foundation for establishing potential benefit, but such studies are not sufficient.

In addition to proof-of-principle studies, we must have clinical outcome studies that follow patients for more than several months and represent the patients and clinical environment in which the therapy will be used. Patients with common comorbidities and with other commonly coadministered therapies should not be excluded. Sample sizes should be large enough to rule out substantial negative effects on morbidity and mortality. Considerable debate has arisen in the clinical community about the appropriate definition of the term “substantial” in this context; however, we cannot afford to allow the complexity of this issue to divert us from the clear knowledge that the effects of therapies for chronic disease often lead to unanticipated outcomes, both positive, as with carvedilol, and negative, as with mibebradil. It is often stated that an approach of determining the outcomes associated with therapies for chronic diseases would be too expensive. A serious effort to streamline clinical trials to reduce the cost while maintaining the sample sizes required to find clinically important differences is urgently needed.

Must the baby be thrown out with the bathwater? In the case of mibebradil, it is difficult to imagine that the compound can be resuscitated specifically for the purpose of limiting infarct size. The clinical setting of myocardial infarction is even more complex than the clinical settings of angina and hypertension, in which the adverse outcomes occurred and led to the withdrawal of mibebradil from the market. Nevertheless, the offsetting negatives of this particular compound should not dampen the enthusiasm for other compounds that block T-type calcium channels, which may hold promise for reducing the size of myocardial infarcts and thereby improving the plight of patients with coronary heart disease. Despite decades of effort to test dozens of pharmacological entities, reperfusion with fibrinolysis or direct mechanical intervention remains the only clinically proven method of limiting
infarct size. Even with the use of these therapies, however, >25% of patients have postinfarction heart failure, and the mortality of these patients is >8% per year. We must continue to focus therapeutic development on solutions to this major public health problem; perhaps other T-type calcium channel blocking agents without the drug interaction problems of mibefradil will lead to reduction in infarct size and improvement in outcomes for our patients.

References

Key Words: Editorials | drugs | trials | myocardial infarction | mibefradil
Good News for Experimental Concept but Bad News for Clinically Effective Therapy
Keith A. Reimer and Robert M. Califf

Circulation. 1999;99:198-200
doi: 10.1161/01.CIR.99.2.198

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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