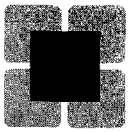

Consequences of the Cardiac Arrhythmia Suppression Trial: calamity or clarity?

THE CARDIAC Arrhythmia Suppression Trial (CAST) was designed to determine whether suppression or elimination of asymptomatic premature ventricular ectopy in patients with a recent, documented myocardial infarction would improve survival during a one-year follow-up period. This large, double-blind, placebo-controlled, multicenter clinical drug study is sponsored by the National Heart, Lung, and Blood Institute (NHLBI).

On April 11, 1989, the Safety Monitoring Board of the CAST reviewed all interim data.[1] The board found, to its surprise, that 56 of 730 patients given the antiarrhythmic agents encainide (Enkaid) or flecainide (Tambocor) and treated for an average of 10 months had died, whereas among 725 patients given a placebo, only 22 had died. The mortality rate of the encainide- or flecainide-treated patients was 2.7 times that of the placebo group.

The independent biostatistical board concurred that these data were significant. Therefore, on April 20, 1989, CAST investigators were advised three days later to discontinue the encainide and flecainide limbs of the study.

Encainide and flecainide had been released by the Food and Drug Administration (FDA) for clinical practice. The two agents were marketed vigorously and were in widespread use. They had been labeled by the FDA for use in two clinical situations: for immediate life-threatening arrhythmias, such as sustained ventricular tachycardia, and for symptomatic but less severe ventricular arrhythmias when the physician considers the benefits of the drug sufficient to outweigh its recognized ability to cause worsened rhythm abnormalities in some cases.[1]

A third antiarrhythmic agent being studied by the CAST, moricizine (Ethmozine), remains classified as investigational. The interim data involving moricizine do not show a statistically significant propensity for increased mortality compared to a placebo.

After conferring with the FDA and the manufacturers, the NHLBI released the preliminary observations and recommended that the encainide and flecainide limbs of the CAST be put on hold. The FDA and the manufacturers in turn urged that encainide and flecainide no longer be used for symptomatic ventricular arrhythmias that are benign or potentially lethal. The labeled indication for immediate life-threatening arrhythmias, such as sustained ventricular tachycardia, remained unchanged, since the CAST data do not relate to patients with this type of disorder.

The FDA and the drug companies notified physicians and the media that they were modifying the labeling for flecainide and encainide, but emphasized that individual treatment decisions must be made by the physician. Physicians were asked to contact patients taking either of the two drugs and to consider whether therapy needed adjustment.[1] Similar notifications were sent to pharmacies throughout the United States.

On April 26, the *New York Times* published a front page report headlined, "Warning Issued on 2 Heart Drugs After Deaths of Patients in a Test."[2] The day after the NHLBI announced the CAST mortality rates, newspaper articles and television spots announced: "Caution Urged on Heart Drugs after Deaths in Tests," "Callers Beseige Doctors," and "Patients Frightened about Heart Drugs." Drug manufacturers estimated that more than 200,000 persons nationwide were taking encainide or flecainide at the time of the announcement.[3] Physicians throughout the world were being asked to provide advice to patients, without having any more in-

formation than the patients.

This sequence of events not only created a storm of anxiety among patients and anger among physicians, but also raised uncertainty and controversy about appropriate medical practice in the light of sparse information published only in the lay press. Initially, the investigators themselves had no better understanding of the preliminary data's implications than the general medical community. However, all data are being analyzed confidentially by the CAST committee and independent statisticians. A scientific report was scheduled for publication in the *New England Journal of Medicine* in late July 1989. Unfortunately, that article is unlikely to provide definite clinical answers or dispel criticisms surrounding this affair.

THE CONTROVERSIES

The CAST-spawned issues include:

1. Was it appropriate for the NHLBI to announce presumed adverse effects of flecainide and encainide through newspapers and television while bypassing the physician?
2. Is the CAST design adequate to appropriately test the hypothesis, randomize patient selection, and provide nonbiased data?
3. Are the clinical implications of FDA labeling (new and old) of flecainide and encainide clear for the following entities: (*a*) postmyocardial infarction asymptomatic ventricular ectopy; (*b*) benign and potentially lethal ventricular ectopy; (*c*) lethal ventricular arrhythmias such as sustained ventricular tachycardia, or ventricular fibrillation and sudden cardiac death; and (*d*) troublesome supraventricular tachyarrhythmias such as atrial fibrillation, atrial flutter, atrioventricular nodal re-entry tachycardia, and Wolff-Parkinson-White syndrome?
4. What is the drug efficacy and tolerance from the clinician's point of view compared to that of the FDA or manufacturer? (i.e., does suppression of premature ventricular contractions mean anything?)
5. Is there a practiced framework from which the clinician can approach the management of ventricular ectopic activity secondary to coronary artery disease? (Sudden cardiac death is not the same as an apparent heart attack.)

DILEMMAS IN DISSEMINATION OF INFORMATION

Predictably, the medical community was angered by not having prior information. The Ohio State Medical Association, for example, submitted an emergency resolution to its House of Delegates for consideration on May 5–7, asking federal and state agencies and other scientific groups to educate physicians before releasing health information of such magnitude to the public.

On the other hand, the NHLBI and FDA are governmental agencies whose purpose is to improve and protect the health of the people. When planning a large-scale clinical trial, the NHLBI uses the following criteria: science, ethics, feasibility, and potential impact. These factors were first tested by the Cardiac Arrhythmia Pilot Study (CAPS).[4–6] Furthermore, the NHLBI and CAST investigators designed the study to employ a safety monitoring committee and biostatistical group totally independent of the investigators and the manufacturers. This permitted periodic evaluation of the data and early identification of statistically significant negative trends related to mortality. From the NHLBI and FDA perspective, a process to alert the physicians independent of the public would have required several months, would have been less complete, and possibly would have been responsible for additional deaths—assuming the CAST observations held true.

The need for rapid dissemination of this information to physicians and patients was further highlighted by the fact that encainide and flecainide had become extremely popular agents for managing supraventricular arrhythmias and suppressing benign premature ventricular ectopy. Their proarrhythmic potential had been minimized in medical journal advertisements disseminated to physicians as part of a large-scale marketing campaign. The NHLBI is obligated by the CAST design to maintain patient safety. The FDA is obligated by law to react to new scientific data regarding released drugs and to subsequently regulate manufacture and use appropriately. The manufacturers are legally bound to comply with FDA rulings.

PRACTICAL IMPACT OF FDA LABELING

Although the FDA does not regulate medical practice, its relabeling created dilemmas for the clinician. The CAST data are limited to patients with prior myocardial infarction and relatively asymptomatic ventricular ectopy; therefore, the remaining recommended use of encainide and flecainide is for patients with life-threatening arrhythmias, such as sustained ventricular tachycardia. In that patient population, the risks of therapy (drug-induced proarrhythmia and congestive heart failure) are higher,[7] yet the risk/benefit ratio of empiric therapy is not well defined for patients with poor left

ventricular function. Furthermore, noncontrolled clinical observations strongly suggest that encainide and flecainide are effective for the management of most supraventricular arrhythmias refractory to quinidine, procainamide, or disopyramide.

The encainide-flecainide risk to patients with nonlethal supraventricular tachycardia is less, but because the risk is still inadequately defined, the FDA has not labeled the 1-C drugs (encainide, flecainide, moricizine) as effective, safe, or appropriate for the management of supraventricular arrhythmias. Before using encainide or flecainide—or even amiodarone (Class III)—for the management of refractory supraventricular tachycardia, the clinician is obligated to carefully assess the relative benefits, uncertainties, and alternative therapies for each individual patient.[8]

The FDA is not supposed to practice medicine; however, in this litigious era, both physician and patient must be aware when using a drug in a manner not recommended by the manufacturer or the FDA. This necessity becomes even more obvious when the FDA and manufacturers reverse themselves and urge that a drug not be used in specific instances.

IMPLICATIONS OF EARLY ARRHYTHMIA TRIAL DATA

The CAST was designed to test the following hypothesis: Use of antiarrhythmic drugs that suppress ventricular ectopy will significantly reduce mortality in patients with asymptomatic ventricular arrhythmias after myocardial infarction. The science, feasibility, and design for the CAST evolved from the last 10 years of NHLBI experience with other projects, including the Multicenter Postinfarction Program (MPIP), the Multicenter Investigation of the Limitation of Infarct Size (MILIS), and the CAPS.[6] From these studies and others, the frequency and severity of ventricular ectopic activity identified patients with a higher mortality risk independent of any relationship to the left ventricular ejection fraction. Age, left ventricular ejection fraction, and frequency of premature ventricular beats were additive in risk stratification. Although some data are available to support specific drug therapy for patients with recurrent sustained ventricular tachycardia responding to programmed electrical stimulation, there are no data to support empiric drug therapy for patients with frequent premature ventricular contractions and nonsustained ventricular tachycardia. The CAPS was initiated to test the feasibility of a larger study; CAPS experience with about 500 patients was used to test and enhance the CAST study design. CAPS was not designed to test the CAST hypothesis or differences in drug efficacy or safety. This makes the bad news from the early CAST data even more compelling.

Preliminary analysis of the interim CAST data seems to indicate the following:

1. As previously mentioned, responder patients receiving clinically appropriate doses of encainide and flecainide had approximately a 2.7 times higher mortality rate than those receiving a placebo.
2. Responder patients on moricizine had no statistically significant difference in mortality compared to a placebo. However, this should not be interpreted to mean that a difference will not become apparent with a larger number of patients and longer follow-up.
3. Suppression of premature ventricular contractions with encainide and flecainide in this subset of coronary artery disease patients did not decrease the risk of arrhythmic death; in fact, it appears to have increased the risk.

Efficacy and safety

The efficacy of a therapeutic intervention must be judged by significant clinical phenomena. When dealing with ventricular arrhythmias, the primary therapeutic goal is to prevent sudden arrhythmic death. Secondary goals are to prevent near-lethal arrhythmic events, such as aborted sudden death and sustained hemodynamically unstable ventricular tachycardia. Efficacy of a drug should not be equated to reduction of premature ventricular contraction or normalization of a Holter recording. The major antiarrhythmic drug risks (adverse effects) include proarrhythmic effect, aggravation of heart failure, aggravation of conduction defects, precipitation of bradycardia, noncardiac organ toxicity, and intolerable nonlethal side effects. A drug-induced arrhythmia (proarrhythmia) may transform asymptomatic premature ventricular contractions to lethal ventricular tachycardia or lower the threshold for ventricular fibrillation during an acute myocardial ischemic episode.

Currently, the FDA limits the labeling recommendation for amiodarone to the management of highly lethal ventricular arrhythmias because of its side-effect profile. Tocainide is similarly limited because of the risk of hematologic dyscrasias. Flecainide and encainide are now limited to the same high-risk patient population because of the CAST data. In contrast, beta blockers have demonstrated improved survival when used in patients with ventricular arrhythmias following myocardial infarction, apparently unrelated to suppression of premature ventricular contraction. Class 1-A drugs (quinidine, procainamide, and disopyramide) and the

Class 1-B drug mexiletine are the only antiarrhythmic drugs currently approved as first-line agents for management of symptomatic but nonlethal ventricular arrhythmias. Their efficacy as it relates to survival remains untested in a controlled setting such as the CAST. The cause of increased cardiac death is not clearly defined by the CAST data. It is hoped that such analysis will be forthcoming.

In patients with so-called lethal ventricular arrhythmias (nonsustained ventricular tachycardia, sustained ventricular tachycardia, or ventricular fibrillation), structural heart disease almost always coexists. In this setting, the proarrhythmic potential for encainide and flecainide increases and patient responsiveness decreases. Decreasing efficacy and increased adverse reactions in those patients most in need of drug therapy is common for most antiarrhythmic drugs. Therapeutic efficacy, as judged by a decrease in total cardiac mortality and sudden arrhythmic death, is most spectacularly improved with implantable defibrillators.[9] The value of rapid defibrillation or cardioversion for lethal arrhythmias is further illustrated in the reported experiences from defibrillation by out-of-hospital emergency medical service teams and by in-hospital defibrillation.[10]

A COMMONSENSE APPROACH

Thus, the therapeutic approach for managing patients at high risk for sudden arrhythmic death following myocardial infarction could be subdivided into primary, secondary, and tertiary therapy:

1. Primary therapy directs interventions toward prevention of coronary artery disease and subsequent myocardial injury.

2. Secondary therapy supposes that myocardial injury has taken place and ventricular ectopy exists due to an abnormal anatomic-electrophysiologic substrate. Those patients without severe left ventricular dysfunction and simple ventricular ectopic activity should be managed with the continuation of primary therapy, beta blockers, and antiarrhythmic agents only for symptom control. Methods to assess vulnerability to more malignant ventricular arrhythmias, such as sustained ventricular tachycardia and ventricular fibrillation, must be undertaken. Risk stratification would include knowledge of the coronary and ventricular anatomy, ischemic response to exercise, extensive Holter monitoring, electrophysiologic assessment with programmed electrical stimulation, and possibly signal averaging. For those patients vulnerable to sustained ventricular tachycardia and ventricular fibrillation, electrophysiologically guided therapy should be initiated.

3. Tertiary therapy involves the use of an implantable cardioverter defibrillator for those patients with lethal arrhythmias or a high vulnerability to lethal arrhythmias despite drug therapy, catheter ablation, and surgical intervention (revascularization and/or electrically guided surgical ablation). The initial cost of this type of therapy is high; however, future cost-benefit assessments will demonstrate device therapy for properly selected patients to be more economical than other therapies. Today, empiric pharmacologic management of benign and potentially lethal ventricular ectopy should be limited to symptom control while avoiding unnecessary risks. Results of empiric management of patients with lethal ventricular arrhythmias are discouraging[11] and should be supplemented with electrophysiologic testing and devices when possible. The use of restricted drugs (amiodarone, encainide, and flecainide) for the management of drug-refractory supraventricular tachyarrhythmias should be limited to those patients who are clearly aware of the risks and other alternative therapies such as surgical and/or catheter ablation.

A commonsense analogy

It is important to understand that primary, secondary, and tertiary therapy are not mutually exclusive. As physicians managing patients with heart rhythm irregularities, our position may be likened to that of the parents of a teenage driver. We know there is inherent potential for danger. Therefore, we insist upon a well-educated driver in a safe automobile (so that most emergencies are prevented), properly functioning anti-locking brakes (to control, suppress, and manage problematic developments), and a seat belt, in case all else fails. The interim CAST data appear to support this commonsense approach.

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