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Commentary

Antiarrhythmic Drugs

Safety First*

Christian Torp-Pedersen, MD, Ole Dyg Pedersen, MD, Lars Køber, MD

Copenhagen, Denmark

"Safety First" was coined in an advertisement for flecainide many years ago. The advertisement was made when the CAPS (Cardiac Arrhythmia Pilot Study) (1) demonstrated that flecainide was highly effective in removing ventricular premature beats from the electrocardiogram in patients who had a prior myocardial infarction. That was a time of innocence and optimism in the area of antiarrhythmic drugs. The innocence and optimism was torn heavily when CAST (Cardiac Arrhythmia Suppression Trial) (2) revealed that the drugs that so effectively reduced post-myocardial infarction arrhythmias were hazardous for patients. But the optimism was not torn completely apart. While the risk of several antiarrhythmic drugs was noted for high-risk patients, it was assumed that they would be safe for patients with few risk factors. Perhaps physicians and even authorities assume that drugs that have been on the market for many years without serious complaints are safe. Recent history has shown this to be wrong. Selective cyclooxygenase (COX)-2 inhibitors were given to millions of patients without serious complaints, and only when trials were scrutinized were the cardiovascular risks revealed (3,4). Diclofenac, one of the most widely used nonsteroidal anti-inflammatory drugs for nearly a generation, is in fact a selective COX-2 inhibitor, and this drug may also be unsafe for patients who have had a myocardial infarction or even for apparently healthy people (5,6). Many years of use of a drug is clearly not a substitute for a formal study of safety.

After the CAST experience, Pfizer developed dofetilide and was required to perform formal studies on high-risk patients to evaluate the safety of the drug (7,8). Even though these trials established acceptable safety, dofetilide was never a huge success, probably because of the risk of torsade de pointes ventricular tachycardia and a complicated dosing schedule.

During the development of dronedarone, Sanofi-Aventis was requested to perform a safety study similar to that of the DIAMOND (Danish Investigations of Arrhythmia and Mortality on Dofetilide) trials, and the ANDROMEDA (Antiarrhythmic Trial With Dronedarone in Moderate-to-Severe CHF Evaluating Morbidity Decrease) ensued (9). The study was based on the DIAMOND-CHF (Congestive Heart Failure) trial design and used an end point that, if used in the DIAMOND-CHF trial as the primary end point, would have come out with significance of benefit. ANDROMEDA was stopped prematurely because of an excess mortality with dronedarone. As rightly pointed out by Singh et al. (10) in this issue of the *Journal*, there is no explanation for the finding. The story of dronedarone might have ended there, but instead, the ATHENA (A Placebo-Controlled, Double-Blind, Parallel Arm Trial to Assess the Efficacy of Dronedarone 400 mg bid for the Prevention of Cardiovascular Hospitalization or Death From Any Cause in Patients With Atrial Fibrillation/Atrial Flutter) trial was conducted and came out with a positive result. This is the first large trial to provide safety data in a moderate risk population that comprises a large part of the relevant patients for rhythm control therapy.

How efficacious is dronedarone compared to other antiarrhythmic drugs for maintenance of sinus rhythm? Dronedarone has been formally compared with amiodarone and was clearly less efficacious in maintaining sinus rhythm. The effect of dronedarone is moderate, as demonstrated in the review by Singh et al. (10), but all antiarrhythmic drugs have moderate efficacy. Any attempt to compare dronedarone with flecainide, sotalol, or other drugs on the market is futile because there are no comparable trials, and comparison with historical data is often misleading. Amiodarone remains the leader among antiarrhythmic drugs in terms of efficacy (11)—other drugs have moderate effectiveness. Thus, in terms of efficacy, dronedarone is probably not a step forward, but whether it is more or less efficacious than flecainide, sotalol, and propafenone when rhythm control is pursued needs to be tested in randomized trials.

How safe is dronedarone compared to other antiarrhythmic drugs? Singh et al. (10) boldly state that flecainide, propafenone, and sotalol are safe for large groups of pa-

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From Gentofte Hospital, Bispebjerg Hospital, and Rigshospitalet, University of Copenhagen, Copenhagen, Denmark. Dr. Torp-Pedersen was on the Steering Committee of the ANDROMEDA study and the ATHENA study, has acted as a consultant for and received consultant fees from Sanofi-Aventis, Abbott, Cardiome, Astellas, Merck, and Novo, and has given lectures at meetings sponsored by Sanofi-Aventis. Dr. Pedersen has received consultant fees from Sanofi-Aventis. Dr. Køber was the primary investigator for the ANDROMEDA study, has given lectures at meetings sponsored by Sanofi-Aventis, is a Steering Committee member of trials sponsored by Novartis, Sanofi-Aventis, and Servier, and is an advisory board member for Novartis and Sanofi Aventis.

tients. It is fair to examine the evidence for such a claim for drugs recommended for the maintenance of sinus rhythm in guidelines (12).

FLECAINIDE. A recent meta-analysis (13) examined the efficacy and safety of drugs for maintaining sinus rhythm. Seventy-one patients were exposed to flecainide in placebo-controlled trials and 132 in trials with a comparator. No deaths were observed. Wehling (14) identified all randomized studies with flecainide involving patients without signs of left ventricular failure. A total of 2,015 years of exposure were found, and there were 8 deaths. Finally, the CAST clearly demonstrated that flecainide should not be used for patients with left ventricular failure (2).

PROPAFENONE. The meta-analysis by Lafuente-Lafuente et al. (13) was able to identify 720 propafenone-treated patients with no deaths in placebo-controlled trials of maintenance of sinus rhythm and 1 death among 152 patients in a comparison with flecainide.

SOTALOL. The meta-analysis by Lafuente-Lafuente et al. (13) identified 30 deaths among 1,391 patients treated with sotalol and 5 deaths among 815 patients treated with placebo ($p = 0.06$). In comparisons with quinidine and amiodarone, there were 56 deaths among 1,316 patients treated with sotalol versus 41 deaths among 1,572 patients treated with amiodarone or quinidine. Also important to note is the post-myocardial infarction trial including 1,452 patients (15) in which sotalol was associated with a statistically insignificant reduction of mortality.

AMIODARONE. The meta-analysis of studies for maintenance of sinus rhythm found 13 deaths among 428 patients randomly allocated to amiodarone versus 3 of 245 patients allocated to placebo ($p = NS$). In comparator trials, there were 38 deaths among 704 patients randomly assigned to amiodarone versus 65 deaths of 704 patients randomly assigned to other drugs. Finally, a series of large studies has demonstrated that amiodarone does not increase death among patients with ischemic heart disease and heart failure (16).

DOFETILIDE. The meta-analysis includes 83 dead among 431 patients randomly assigned to dofetilide and 83 among 245 patients randomly assigned to placebo. The high mortality reflects that selected patients from the DIAMOND studies (7,8) were included. The DIAMOND studies included >3,000 patients in total with left ventricular dysfunction and either heart failure or a recent myocardial infarction. These studies were neutral with respect to mortality.

DRONEDARONE. Four placebo-controlled studies of atrial fibrillation used a dronedarone dose of 800 mg daily (17–19). In total, these document 125 dead among 3,214 patients randomly allocated to dronedarone and 142 deaths among 2,825 randomly allocated to placebo. The ANDROMEDA study conducted with heart failure patients was terminated early because of increased mortality. Dronedarone reduced cardiovascular hospitalizations among patients by 24% in the ATHENA study, and such a direct clinical benefit has not been demonstrated for any other antiarrhythmic drug.

Singh et al. (10) provide many calculations of 95% significance interval for mortality in various subgroups treated with dronedarone. It should be noted that any attempt to make such calculations for other available antiarrhythmic drugs would result in confidence limits that include very high risks. If "safety first" is the issue, the data for dronedarone are superior to those of other antiarrhythmic drugs for low/moderate-risk patients.

Does dronedarone change the rate versus rhythm treatment option? Two large trials have shown equivalence between rate control and rhythm control therapy, with rhythm control mostly based on treatment with amiodarone (20,21). While insignificant, the balance was slightly in favor of rate control therapy. Singh et al. (10) consider rate control therapy the first choice for many patients, which is probably correct for those who are eligible for the preceding studies. Nevertheless, rhythm control is the chosen therapy for many patients. The problems arise when an antiarrhythmic drug is considered necessary to maintain sinus rhythm or is preferred by the patient. So far, decent advice would require that patients are informed of the unknown safety of most compounds and of the common problems with long-term amiodarone therapy. With dronedarone, it is for the first time possible to provide reassurance to large groups of low-risk patients. More patients will possibly accept antiarrhythmic therapy to maintain sinus rhythm.

Which drugs are first-line therapy for maintenance of sinus rhythm in atrial fibrillation? For patients with heart failure, dronedarone brings no news. Dofetilide and amiodarone are still the only drugs with proven safety for these patients. For intermediate-risk patients, dronedarone provides another option with an uncertain placement. Although dronedarone should clearly not be used for patients with severe heart failure, the safety of most antiarrhythmic drugs for intermediate-risk patients is uncertain. For patients with low risk, dronedarone provides the only antiarrhythmic drug with a large safety database to prove reasonable safety. The safety knowledge of dronedarone may result in patient and physician preference of dronedarone as first-line therapy, with a possible switch to amiodarone when sinus rhythm is no longer maintained.

Reprint requests and correspondence: Dr. Christian Torp-Pedersen, Department of Cardiology, Gentofte Hospital, University of Copenhagen, Niels Andersens Vej, 2900 Hellerup, Denmark. E-mail: ctp@heart.dk.

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