Dofetilide: what role in the treatment of ventricular tachyarrhythmias?

See page 2180, doi: 10.1053/ehj.2001.2679 for the article to which this Editorial refers

In the present issue Boriani et al. report the results of a prospective double-blind randomized crossover study, in which the short- and long-term efficacy and safety of oral dofetilide or oral sotalol were compared in 135 patients with ischaemic heart disease and inducible sustained ventricular tachycardia.

Dofetilide was as efficacious as sotalol in preventing the induction of sustained ventricular tachycardia, which was achieved in one third of the patients. There was no concordance in the response to the two drugs. During the acute phase dofetilide was significantly better tolerated than sotalol. However, during long-term treatment, which was not randomized, both drugs were well tolerated.

This study is based on the use of electrophysiologic testing as a guide for selecting antiarrhythmic drug therapy in ventricular tachyarrhythmias, a

References
classical approach\cite{2,3} that in recent years was dramatically challenged by the use of implantable cardioverter-defibrillators\cite{5,5}. With this in mind, the study should be considered as reflecting an approach (i.e. a serial electrophysiological study for selecting antiarrhythmic therapy on the basis of suppression of ventricular tachyarrhythmia inducibility) that is outdated. Nevertheless, this study is interesting, especially considering the very small number of studies on antiarrhythmic drug therapy currently published.

Although AVID\cite{4} showed that in survivors of ventricular fibrillation or in patients with sustained ventricular tachycardia causing severe symptoms, the implantable cardioverter-defibrillator is superior to amiodarone or sotalol for increasing overall survival, subsequent studies and a recent meta-analysis showed that the benefit conferred by device therapy was not confirmed for patients with well-preserved left ventricular ejection fraction\cite{6-7}.

In view of these considerations in clinical practice, there may still be a role for antiarrhythmic drug treatment in the management of ventricular tachyarrhythmias: for prevention of ventricular tachycardia recurrences in patients with well tolerated sustained ventricular tachycardia or in patients with symptomatic non-syncope sustained ventricular tachycardias and left ventricular ejection fraction >40%, two populations which are not included in AVID. Drugs may also be useful for reducing ventricular tachycardia recurrences in patients who already have an implantable cardioverter-defibrillator. These points are of particular importance in countries where the actual cost of implantable cardioverter-defibrillators has limited the number of implanted devices\cite{8,9}.

The ESVEM study was the only study to use an electrophysiologically guided strategy to compare the efficacy and safety of alternative antiarrhythmic drugs in patients with ventricular tachyarrhythmias\cite{10}. The efficacy of different class III antiarrhythmic agents in particular, in patients with ventricular tachyarrhythmias had not been previously assessed by a randomized crossover study using electrophysiologically-guided treatment, such as the study reported by Boriani et al\cite{1}. Dofetilide is a selective IKr channel blocker\cite{11} approved by the Food and Drug Administration for the treatment of atrial fibrillation and effective for treating and preventing a broad range of supraventricular and ventricular tachyarrhythmias\cite{12-44}. This drug has been shown to be effective in preventing the induction of sustained ventricular tachycardia in approximately 30% to 40% of cases, a finding that is confirmed in the present study\cite{13}.

The results of this study demonstrate that dofetilide and sotalol have equal efficacy, as determined by PES, but that dofetilide has a lower rate of adverse events with short-term therapy. This is a clinically relevant result because sotalol was the most effective drug in ESVEM\cite{10} and did not differ from amiodarone in another study\cite{15}. Sotalol, in its currently used racemic form, did not differ from placebo in a post-infarction mortality trial\cite{16}. Although dofetilide had a neutral effect on survival in the DIAMOND study\cite{14}, the major concern in the use of any IKr blocker remains the risk of torsades de pointes. It has recently been shown that a stepwise approach, combining in-hospital therapy initiation, pre-dose adjustment for renal function, and post dose adjustment based on QTc lengthening during ECG monitoring, reduced the rate of torsades from 3-1% to 0-4% in patients with supraventricular arrhythmias\cite{17}. Based on the findings of the present study and its lack of negative inotropic effects, dofetilide may prove to be an alternative to sotalol treatment in ventricular tachyarrhythmia treatment, with comparable efficacy but better tolerability.

In the study by Boriani et al. there was no concordance in the response to dofetilide or sotalol\cite{1}. Indeed, two-thirds of the patients, in whom ventricular tachyarrhythmia inducibility was suppressed, responded to only one of the two drugs. There may be a different interpretation of this finding, including a different effect on the electrophysiological substrate; nevertheless, the clinical implications are really relevant because the response at electrophysiological testing cannot be considered simply as a ‘class effect’ and testing a second class III antiarrhythmic agent may increase the response rate to 52%\cite{3}. Moreover, in this study the lower rate of withdrawals during long-term follow-up in dofetilide-treated patients compared with sotalol strongly supports the clinical usefulness of this new drug. The limitations of sotalol with regard to tolerability have been previously stressed\cite{18,19}; both a high rate of sotalol discontinuations (33% at 1 year)\cite{18} and a relevant incidence of crossover to other treatments (27% within 3 months of treatment)\cite{19} were found.

A recent study by Mazur et al.\cite{20} suggests that in patients implanted with a cardioverter-defibrillator, treatment with dofetilide modified the pattern of ventricular tachyarrhythmia recurrences in comparison to placebo, with an increase in pause-dependent polymorphic ventricular tachycardias, a reduction in multiple episodes of monomorphic ventricular tachycardia and an increased effectiveness of antitachycardia pacing interventions. In the editorial commenting on this paper, Lauer reports that, in his view, dofetilide may find its most useful niche in the treatment
of ventricular tachyarrhythmias in patients with cardioverter-defibrillators\cite{21}. This point of view is of course strengthened by the results of this study. As a general comment, we also agree with the concept that regardless of the revolutionary therapies of interventional cardiology there will always be a need for effective and safe antiarrhythmic drugs. Indeed, patients with frequent appropriate cardioverter-defibrillator interventions or with unsuccessful ablative attempts will continue to require some sort of palliative antiarrhythmic treatments.

Although the study reported by Boriani et al.\cite{11} was not designed to evaluate the impact of antiarrhythmic drugs on mortality, it is noteworthy that in patients selected for long-term treatment on the basis of the response to electrophysiological testing in the acute phase, the occurrence of arrhythmic death was very low (only one arrhythmic death at 1 year).

According to the study reported by Boriani et al.\cite{11} and the results of the DIAMOND study\cite{14}, dofetilide may be considered an effective and clinically useful drug, which may also be used in patients with ventricular tachyarrhythmias. A randomized study against the automatic implantable cardioverter defibrillator would certainly be welcome in the near future.

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References