SCIENTIFIC EDITORIAL

Dronedarone: From buzz to reality

Dronédarone : du buzz à la réalité

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Recently, a great 'buzz' has surrounded dronedarone — the new benzofuran antiarrhythmic drug developed for the treatment of atrial fibrillation.

The development of dronedarone has been protracted and complex. The main reason for the complexity is not related directly to the compound, but to the pathology of the disease. Atrial fibrillation is an independent factor for increased mortality and morbidity [1]. Nevertheless the life expectancy of most patients suffering from atrial fibrillation remains high, and it is very difficult to demonstrate an effect of a drug on "hard" endpoints in atrial fibrillation trials, whatever the type of the therapy, pharmacological or not. Indeed the occurrence rate of events remains low and it is necessary to do trials with a huge number of patients and/or a long follow-up period.

Furthermore, arrhythmias are complex and multiform. Unlike some other fields of cardiovascular therapy, the treatment of arrhythmias cannot be managed by a single drug [2]. Antiarrhythmic drugs may act on many targets, including various ionic currents, but also receptors and pumps. In most cases, it is much easier to control hypertension or lipid concentrations than it is to control arrhythmias! Finally, atrial fibrillation is the arrhythmia whose mechanisms are the most complex, involving four pulmonary veins, two atria and two vena cava, and these mechanisms may mix abnormal foci, conduction disturbances, rotors and ganglionic plexi! In most instances, atrial fibrillation occurs in elderly patients with multiple comorbidities such as hypertension, coronary artery disease, heart failure, valvulopathies, cardiomyopathies, sleep apnoea syndrome or obesity...
For about 20 years, the safety of antiarrhythmic drugs used in the maintenance of sinus rhythm in atrial fibrillation patients has been questionable [3]. Following publication of the Cardiac Arrhythmia Suppression Trial in 1989 [4], Coplen et al., in a meta analysis published in 1990, showed that quinidine treatment was more effective than no antiarrhythm ic therapy in suppressing recurrences of atrial fibrillation, but appeared to be associated with increased total mortality [5]. In the past 20 years, this major safety problem has been evoked for all other antiarrhythmic drugs, even if it was already clear at the time that the safety profile of quinidine itself could be unfavourable compared with other antiarrhythmic drugs, mainly due to the risks of QT prolongation and **torsades de pointes** induced by the drug. For these past 25 years, no other new oral antiarrhythmic drug has been developed successfully for atrial fibrillation, with the exception of dronedarone. Atrial fibrillation is a serious disease that can alter the patient’s quality of life and increase mortality, which is a major burden for healthcare systems [6]. Nevertheless, the mortality rate of atrial fibrillation remains low, around 3% per year, and it is very difficult to demonstrate, knowing this low mortality, a gain in terms of morbimortality.

The results of the ATHENA study demonstrated a decrease in the combined endpoint [7], i.e. hospitalisations for a cardiovascular reason and total mortality, with dronedarone treatment. It is not possible to consider that this success, never obtained with any other drugs for the past 25 years, can be offset by the fact that dronedarone also has limitations. The main limitation of dronedarone is its safety in patients with heart failure. Dronedarone may be safe to use in patients with hypertension, including those with left ventricular hypertrophy and in patients with coronary artery disease, as clearly demonstrated in the different trials involved in the development of dronedarone, mainly ATHENA. For heart failure, the situation is more complex. The results of ANDROMEDA were not in favour of dronedarone [8], so it should be used with caution in this population. The labelling obtained from the Food and Drug Administration and from the European Medicines Agency excluded patients with NYHA class IV heart failure and patients with unstable heart failure. In order to obtain the best results with the drug, it is necessary to prescribe it with caution and to avoid its use in patients with class IV but also with class III heart failure. Indeed a large proportion of patients with class III heart failure can also be those with unstable heart failure.

A lot of buzz currently surrounds dronedarone, including surprising publications using data from the DIONYSOS study, which had not been published [9,10]! It is without doubt questionable to include data from a press release in a meta-analysis [9]. The role of the reviewers and the editors of prestigious, high-impact journals is to be rigorous in ensuring accepted articles are based on robust data and appropriate methods and protocols. The results of DIONYSOS [11] – a head-to-head comparison with amiodarone – were not in favour of dronedarone. The design of the trial was original, mainly concerning the primary composite endpoint mixing recurrences of atrial fibrillation and premature study drug discontinuation. Indeed, the efficacy of amiodarone is well known, but the problem in treating patients with this drug is the necessity, in a large proportion, to discontinue the drug because of side effects, mainly extracardiac, and in most cases, involving thyroid events. The median treatment duration in DIONYSOS was very short, i.e. 7 months. This brief follow-up was chosen to enable the company developing dronedarone to include the study in the registration dossier. It was impossible to hope that the results would favour dronedarone, however, as a short follow-up is insufficient to demonstrate superiority over amiodarone, knowing that the discontinuation of amiodarone occurs, in most of the cases, after its extended use; a follow-up of at least 2 years would have been necessary. The side effects of amiodarone are frequent and generally appear after several years of use. It is impossible to consider, as done by the transparency commission in France, that dronedarone does not represent an advance compared with amiodarone. Indeed, if a marketing authorization for a drug similar to amiodarone had been submitted in recent years, it would have been rejected for sure! No benefit has been observed with amiodarone in terms of morbimortality in atrial fibrillation patients. Recently, Andersen et al. [12] published data from a large, unselected, population-based cohort of patients discharged with first-time atrial fibrillation and subsequently treated with flecainide, propafenone, sotalol or amiodarone. The results were based on data obtained in 141,500 patients included in this nationwide Danish registry. A higher annual mortality rate was observed with amiodarone. It is possible to hypothesize that these data are due both to the poor safety of amiodarone and the severity of the underlying diseases of patients for which amiodarone was chosen.

The reality is that dronedarone is a real novelty, after a 25-year absence of new antiarrhythmic drugs for patients with atrial fibrillation, and the limitations of dronedarone are clearly not so important as those of amiodarone.

**Conflict of interest statement**

Dr Le Heuzey was the principal investigator of the DIONYSOS trial, funded by Sanofi Aventis.

**References**


