OPINION ARTICLE

There is as space for the pharmacologic treatment of arrhythmias?

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XXI Century finds us with a change in the paradigm of cardiac arrhythmias treatment. Given that sudden death is caused by severe ventricular arrhythmias, and cerebrovascular accidents (CVA) are caused by severe incapacitating or fatal supraventricular arrhythmias – atrial fibrillation – it was natural to suppose that antiarrhythmic drugs could reduce such mortality.

I refer to those antiarrhythmic drugs we have for over 40 years and are still the same and are classified with Vaughan & Williams scheme (Table 1). Some of those drugs, as dofetilide, did not appear in the Argentine market and others, as mexiletine had disappeared.

Things changed over the years, and at the end of the eighties and early nineties, CAST, a multicentric study with more than 1400 patients listed to assess the usefulness of the administration of antiarrhythmic drugs in post-myocardial infarction patients, showed that instead of reducing mortality given the antiarrhythmic effectiveness of the used drugs (flecainide, moricizine, encainide), it was significantly increased. The study was interrupted with a placebo significant advantage. (1)

Large multicenter studies which showed the uselessness of antiarrhythmic drugs to reduce mortality, especially sudden death, appeared. Studies such as MUSTT (2) did it with more accuracy selecting the drugs according to the effectiveness through electrophysiological inducibility. This selection allowed better results than placebo use, but did not reduce mortality compared with the automatic implantable cardioveter-defibrillator (AICD).

Since then, a large number of studies were performed, so from 1993 to 2008 AICD implantation increased 20-fold. Only two studies, CABG-Patch and Dinamit, showed that the drugs were more effective in reducing mortality, in one case because myocardial revascularization was more effective, and in the other case due to its early implantation in relation to the AMI.

Even the most effective antiarrhythmic drug -amiodarone-, though with more undesirable side effects, showed in large studies as SCD-Heft that it was as effective as placebo in the primary prevention of total mortality, provided that all the patients were well treated, particularly with beta-blockers. (3)

Table 1. Vaughan & Williams classification

Class I	Class II	Class III	Class IV
Quinidine			
Procainamide			
Lidocaine	Beta-blocker	Amiodarone	Verapamil
Mexiletine		Sotalol	Diltiazem
Flecainide			
Propafenone			

However, we wondered why scientists continue investigating so many new drugs with new mechanisms? Dozens and dozens of new drugs are being tested. Some of them have already been approved and entered the medical world. They can be found in three groups: those that take action on transmembrane rectifying potassium channels present in auricles or on serotonin receptors and others that act on several ion channels, which contrary to the previous ones involve the risk of having severe arrhythmias – polymorphic ventricular tachycardias and the so called in tip torsion -, in most of the cases due to QT prolongation or alterations in ventricular repolarization, this risk is absent in the previous group since it only takes place at auricular level. And finally, the group of drugs with diverse mechanism, as it is the exchange sodium/calcium or sodium/hydrogen, etc. (Tables 2, 3 and 4).

However most of these drugs are not better than placebo in the prevention of sudden death or total mortality, and even they increase the presence of severe arrhythmias. An example of those is the azimilide, which in ALIVE study, in more than 4.200 patients, against placebo, showed that there were no differences in mortality and even if it reduced the presence of sustained and non-sustained ventricular tachycardia, showed a high rate of polymorphic ventricular tachycardia. Drugs which already are in the markets of central countries, as dofetilide or ibutilide, also have a significant incidence of severe arrhythmias despite being effective as antiarrythmics. (4)

These and others studies demonstrated that antiarrhythmic drugs at ventricular level are reserved for the symptomatic treatment of benign ventricular arrhythmias, that are present in hearts with no heart disease, with good ventricular function, not inducible in electrophysiology laboratory and of low risk. In malignant arrhythmias – ventricular tachycardia and ventricular fibrillation – are not more useful than the implantation of an AICD. Regarding the intermediate group, the potentially malignant arrhythmias – non-sustained ventricular tachycardias, frequent, polymorphic or in pairs, etc. ventricular extrasystoles-, in patients with heart disease, most of them with low ejection fraction, or inducible, the usefulness of antiarrythmics including amiodarone, is debatable and should be selected carefully in each case.

Regarding supraventricular arrhythmias they did not show being totally effective in the prevention of severe tachyarrhythmia, atrial fibrillation (AF), due to their incidence in the generation of CVA and disabilities or as consequence of the ventricular high response. In the field of secondary tachyarrhythmia to re-entrant circuits, transcatheter invasive treatment, by ablation with different energy sources, showed that is more effective, and even in some cases curative.

In AF, antiarrhythmic drugs have limited

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Table 2. Drugs that block auricular ion channels

Agent	Mechanism of action
MPS	I_{Kur}
JTV 519	I_{KACH} I_{Kr}
S1185, S9947, S2091	I_{Kur}
AVE 0118	I_{kur} I_{to} I_{KACH}
RS 100302	5-HT_4
RSD 1235 (vernakalant)	I_{kur} I_{to} I_{KACH}

Table 3. Drugs that block multiple ion channels

Agent	Mechanism of action
Dronedarone	I_{kr} I_{Kur} I_{to} I_{Ka} I_{Na} beta-blocker
Celivarone	I_{kr} I_{Kur} I_{to} I_{Ka} I_{Na}
Ambasilide	I_{kr} I_{kur} I_{Ka}
Azimilide	I_{kr} I_{Ka}
Tedisamil	I_{kr} I_{Kur} I_{to} I_{Ka} I_{KATP}
ATI-2042	I_{to} I_{ka} I_{kr} I_{Ka} I_{Ca}
Ranolazine	I_{kr} I_{Na}
AZD 7009	I_{kr} I_{kur} I_{Na}

Table 4. Other new antiarrhythmic drugs

Agent	Mechanism of action
CPO 605	Na^+/Ca^+ Exchange inhibitor
RS 6865	$Na+/Ca^+$ Exchange inhibitor
KB-R 7943	Na^+/Ca^+ Exchange inhibitor
GsMtx4	Stretch receptor antagonist
AAP10	Modifies conduction of gap junctions
ZP123	Modifies conduction of gap junctions
Abanoquil	α 1^a antagonist
Cariporide	Na^+/H^+ Exchange inhibitor
E 3174	Angiotensin II antagonist
KB 130015	Thyroid antagonist
L 768673	I_{ks}

effectiveness in its prevention, thus they show a recurrence, even associated, of 40% to 50% annual. Once more, the most effective drug, amiodarone, showed an effectiveness of about 70% in the maintenance of sinus rhythm at 2 years.

Vernakalant (RSD 1235) is not yet an approved drug but showed effectiveness in the reversion of acute episode with 45% of reversions against about 15% of spontaneous reversion. It is important to mention that mean of reversion time was 12 minutes. However, when used as prevention of recurrence it was not better than the rest of the antiarrhythmic drugs: about 40% continued in sinus rhythm at 100 days. (5)

The studies performed to assess the effectiveness of dronedarone, which is already in central countries markets and will soon be in South America, showed interesting results.

The studies performed to know the safety, effectiveness and the necessary dose of dronedarone (DAFNE study) did not show a different rate than the mentioned antiarrhythmic drugs. The dose of 800 mg showed that between 40% and 50% of the patients maintained in sinus rhythm at six months. (6) Two studies were performed to know the effectiveness of 800 mg in two doses: Euridis in Europe and Adonis in Australia and America –even in our country- where 1.200 patients were included in a follow-up at 1 year in a proportion of 2:1 for effective drug. These studies showed a reduction of 25% in AF recurrences at 1 year in patients who had showed an episode within six months.

A prolongation of more than two times was observed at the time of the recurrence. (7)

Another interesting point was that in those patients in whom arrhythmia was recurrent, the ventricular response was significantly lower. The undesirable effects were not important, mainly by not incorporating iodine molecules that are in the amiodarone; a higher incidence of hyperthyroidism was observed in the placebo group with regard to dronedarone. The only remarkable side effect was the increase of creatinine.

If we compare amiodarone with dronedarone, regarding antiarrhythmic effectiveness, the first one is better, whereas mortality is similar. However, regarding undesirable side effects, amiodarone is better than dronedarone. (8)

In another study which included patients with severe ventricular dysfunction, more than a half in class III and IV, the investigation had to be interrupted as higher mortality in the active group was observed. It was a group treated with beta-blockers, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, diuretics in a good proportion with spironolactone and digital; a third of them anticoagulated. (9)

The larger research in atrial fibrillation with more than 4.600 patients was carried out in the study called ATHENA. (10) This study completes the change in the paradigm in the treatment of atrial fibrillation with antiarrhythmic drugs.

They were carriers of paroxysmal or persistent atrial fibrillation with at least one risk factor for death: controlled hypertension with at least two drugs, heart failure, diabetes, CVA or TIA, elderly. It also included 4% of patients with ejection fraction lower than 35% but stable and controlled.

The treatment was the appropriate, including 60% of anticoagulated in adequate range. Those patients with heart failure class IV or pulmonary oedema 12 hours before, in shock, with vasopressors or in respirator, significant, obstructive hypertrophic valvular disease or recently operated were excluded.

The endpoint was death or hospitalization, which showed a reduction of 24%. Although it did not reduce total mortality, a decrease in cardiac mortality and hospitalizations was observed. Although the cause of hospitalizations was heart failure, CVA, syncope or ventricular arrhythmia, undoubtedly atrial fibrillation was the most significant cause of hospitalization reduction. The incidence of CVA, as well as acute coronary syndrome and cardiovascular mortality was notably reduced. (11)

This drug, and probably others which would come, reduced in a significant way the time of cardiovascular or other cause hospitalization, cardiovascular mortality, antiarrhythmic death and the incidence of CVA.

If we consider that in a near future we would have more reliable anticoagulant drugs and with less undesirable effects and easier in their administration,

with no frequent and complicated controls, it is clear then that in the field of supraventricular arrhythmias the paradigm had changed. Again, those invasive procedures like ablation as well as the use of antiarrhythmic drugs are reserved for symptomatic or uncontrollable patients.

The current researches in antiarrhythmic treatment suggest that there would always be a place for drugs, but the current objectives are changing.

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