AJMALINE HYDROCHLORIDE: IT'S MULTIPLE DIAGNOSTIC-THERAPEUTIC USES AND ITS VALUE IN BRUGADA SYNDROME

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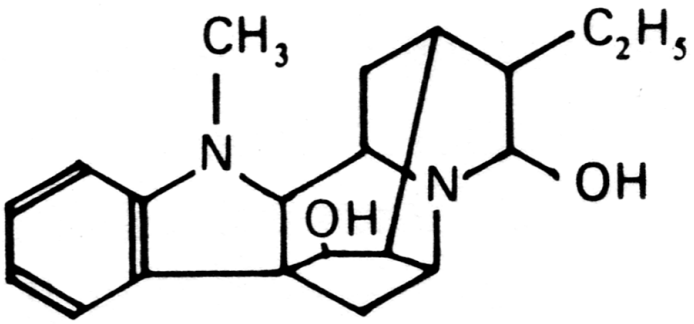
Structure: Alkaloid derived from the Rauwolfia serpentina[1], about which a first report was presented recently, regarding the production of hairy root cultures of the micrantha root of the Rauwolfia [2].
A new enzyme, the 1,2-dihydrovomilenine reductase, was detected in suspension cultures of Rauwolfia cells. The enzyme converts the 2beta(R)-1,2/ dihydroovomilenine by a reaction dependent on NADPH in 17-O-acetylnorajmaline, a near precursor of the antiarrhythmic alkaloid ajmaline, derived from the Rauwolfia[3].
The structure of the drug is +-17R-O-(3',4',5'-trimethoxybenzoyl) ajmaline[4].



AJMALINE

Class: It belongs to class 1A of the Vagham Williams classification. This group is characterized by causing a moderate block of the fast Na^+ channels, and they display and intermediate binding and release kinetics with the channel (1 to 5 seconds). They reduce the V_{max} (less conduction velocity) and prolong the action potential (AP). Ajmaline differs only in the His-Purkinje system, causing a significant shortening of the dome, plateau or phase 2 of AP.
The other class 1A drugs are quinidine, procainamide, and disopyramide phosphate.
This is partially a quinidine-like drug; however, unlike the latter, it does not cause a block in the I_{to1} channel, transient outward K+ current or 4-AP-sensitive current. This fact is responsible for the opposite effect on the repolarization of both drugs in Brugada syndrome: ajmaline worsens and quinidine improves[5].

Brand name: absent in our country and in USA.

Presentation:
50 mg pills. Monochlorajmaline: 200 mg pills. 50 mg ampoules.

Pharmacokinetics:
Absorption: the presence of renal failure has been verified to increase the initial rate of absorption of the drug in the small intestine of rats[6].
Oral:
Dosage: 1 to 2 pills of 6/6h.

Peak of plasma concentration in oral administration: 1 minute.

Half life T1/2: extremely brief: seconds. After 1 minute a 10% remains, in 5 minutes 2.5% and in 30 minutes only 0.5%.
EV:
Presentation: 50 mg ampoules.

Dosage: 50 mg/EV in 10 to 30'' or 10 mg each 30''

Maximal dose: 1 mg/Kg administered in 5 minutes by perfusion of 0.25 mg/Kg in 15 minutes.

Organs that metabolize the drug: the ajmaline derivatives are chloroacetylated esters: monochloroacetyl ajmaline and dichloroacetylajmaline have antiarrhythmic properties.

Electrophysiological mechanisms of action: Electrophysiological mechanisms of action
Modifications on ECG:

Heart rate: mainly, it acts by an indirect autonomous effect, causing catecholamine depletion, which in turn could cause a non-significant increase with RR shortening[12]. Additionally, it has a direct depressor effect on the membrane. Sinus dysfunction has rarely been described.

P wave: it increases in duration, which could lead to a mistaken diagnosis of left atrial overload (LAO) by increase of the PA interval.

PR interval: It causes a prolongation by moderate increase of the AH interval.

QRS duration: Constant prolongation as a consequence of negative dromotropism, more intense in the His-Purkinje system. This effect is more pronounced with ajmaline hydrochloride than with derivatives. It is contraindicated in patients with preexisting prolonged QRS. In patients with ventricular preexcitation of the WPW type, it extends the effective refractory period of the Kent bundles, showing the characteristics of the baseline ECG tracing, which allows:

a) Revealing the possible association with ventricular hypertrophy, electrically inactive areas, bundle branch blocks, etc;
b) In the case of WPW disappearance, it allows inferring that the accessory pathway has a relatively long refractory period (benign);
c) When there is more than one accessory pathway with different refractory periods, the block of the pathway with the longest refractory period allows revealing the existence of another pathway.

QTc interval: it is prolonged, and it could rarely cause torsade de pointes (TdP).

Accessory pathways: it significantly prolongs the effective refractory period of the Kent bundles, and it could nullify the WPW pattern in tracings.

Indication of ajmaline:
It has two purposes:

a) Diagnostic
b) Therapeutic

a) Diagnostic

I) For the diagnosis of concealed forms and transitory or intermittent forms of Brugada syndrome
II) In patients carriers of symptomatic bifascicular blocks (fainting, syncopes or Adams Stokes), in whom there is a suspicion of the presence of a high-degree AV block, intermittent and paroxysmal as a cause;
III) If administered through the EV via and acutely in patients with implanted pacemaker, it could cause a significant decrease of the response of amplitude provoked, remaining in a mean 6 minutes. Changes of polarization were not observed;

IV) Administered through the EV via and acutely in patients with implanted pacemaker;
V) As a test to infer whether another approach would be necessary in ICD implantation;
VI) As diagnostic test before suspicion of latent forms of myocarditis during the indeterminate stage of the disease.

I) For the diagnosis of concealed forms and transitory or intermittent forms of Brugada syndrome;

In many patients with Brugada syndrome the typical ECG manifestations may become normalized transitorily, leading to diagnostic difficulties. The administration of class IA sodium channel blockers, ajmaline and procainamide, and class IC drugs, flecainide and pilsicainide, emphasize the ST segment elevation and could unmask concealed and intermittent forms[13]. The drug is used through the EV via, in a 10 mg dose each two minutes, until it reaches a 1 mg/kg dose. A prolongation of > 30% of the QRS complex, the appearance of a typical pattern or extrasystoles, are considered events that indicate the end of the test[14].

The responses could be varied:

1) In approximately 20 to 25% of the cases, a typical coved ST segment elevation pattern appears, at least 2mm in at least two right precordial leads from V1 to V3, which means the test is positive. In a patient with ECG that suffered aborted sudden cardiac death or syncope, without structural heart disease, if ajmaline causes this ECG pattern, automatic cardioverter defibrillator implantation is indicated[15-16-17];
2) There is a reference to the appearance of extreme deviation of SAQRS to the left in the frontal plane, concomitant with ST segment elevation. The phenomenon probably reflects a left anterior fascicular block due to the predominant effect of the drug on the His-Purkinje system[18];
3) The test may differentiate the cases of arrhythmogenic RV dysplasia, where the ST segment elevation with use of class IA antiarrhythmic agents, ajmaline and procainamide (ajmaline 1 mg/kg), procainamide (10 mg/kg) or class IC (flecainide 2 mg/kg) do not cause elevation[19];
4) In some patients previously classified as having IVF, the test of ajmaline or procainamide unmasks the typical ECG Brugada pattern, suggesting that this incidence could be higher than what was suspected previously[20];
5) In Brugada syndrome, the EV test of ajmaline, concomitantly with ST segment elevation in the right precordial leads, a delay is observed in the zero phase (upstroke) of the

monophasic action potential (MAPs) exclusively or more pronounced in the RV outflow tract[21];

6) Symptomatic VT (rare, less than 1.5%)
7) Monomorphic VT has been described after injection of ajmaline in Brugada syndrome[22];
8) In patients carriers of Brugada syndrome, the area estimated of ST segment elevation, using body surface potential mapping, in the presence of posterior potentials and certainty at PES, constitutes a valuable non-invasive marker in risk stratification; and when ajmaline is used, this estimated area of ST segment elevation increases even more[23];
9) Using body surface potential mapping, it was observed that in left precordial leads, the patients with Brugada syndrome showed the mirror or reciprocal image of the shifts occurred in the right precordial leads, and these shifts are increased when ajmaline is used[24];
10) ST segment elevation has rarely been observed from V_1 to V_2 without arrhythmias, which may mean silent ischemia not detected previously, transmural dispersion of conduction and refractoriness in the RV outflow tract or HR-dependent sodium channel block[25];
11) In patients with normal baseline ECG, approximately 2% of the cases, the test results positive. **The test is indicated in all patients that suffered aborted sudden cardiac death or unexplained syndrome, without structural heart disease, in whom the ECG would not spontaneously show the typical ECG Brugada Type 3 pattern(normal or Types 1 or 2). Also, in the relatives of the affected patients. The test with this drug in Brugada syndrome is considered a very useful tool**[26].

II) In patients carriers of symptomatic bifascicular blocks (fainting, syncopes or Adams Stokes), in whom there is a suspicion of AV block presence, of high degree, intermittent and paroxysmal as a cause

The drug allows the diagnosis of paroxysmal AV block by bilateral lesion of the conduction pathways or more rarely, in the His bundle branch, unmasking latent conduction alterations, generating symptoms of low brain flow, such as fainting, syncope and Stokes Adams: intermittent AV block[27].

Methodology:

Objective: measurement of degree of worsening of atrioventricular block.

1) Administer 50 mg EV in 3 min
2) Repeat the same dose after 3 min if conduction persists 1:1

3) Ventricular stimulation 20 bpm above sinus rhythm for two minutes, and abrupt suppression.

Criterion for test positivity:
Appearance of AV block of second or third degree.
Increase in HV duration = or > than 100% of basal value. Four types of response have been reported: HV interval > 80 ms; between 80 and 10 ms (risk of atrioventricular block 35.5%); > 100 ms (risk of atrioventricular block 62.5%) and distal block (risk of atrioventricular block 100%). The indication or not of pacemaker implantation depends on the result of this test.
Contraindications to make this test:

1) History of recent infarction;
2) Heart failure;
3) Significant cardiomegaly.

Specificity: 70%
Sensitivity: 85%
Asymptomatic patients with branch block with positive test, would be in a higher risk of developing a high degree AV block, if the A-H interval gets prolonged > 100 ms. It is indicated only in patients that had syncope, Adams-Stokes episode or fainting[28]. The test must be carried out only after implanting an electrocatheter in the RV, connected to a demand pacemaker due to the risk of causing long-duration asystole or third-degree AV block with Stokes Adams.

IV) Administered through the EV via and acutely in patients with implanted pacemaker

It may cause a significant decrease of the amplitude response provoked, remaining 6 minutes in average. Polarization modifications are not observed[29].

V) As a test to infer whether another approach would be necessary in ICD implantation

In Brugada syndrome, changes spontaneous or induced by ajmaline in surface ECG, may cause in a parallel way, significant variations in the endocardial electrogram of the RV outflow tract, resulting in an ICD malfunction. The epicardial implantation in the LV to detect and pace, could be a good approach in some specific patients. Ajmaline could be helpful during an ICD implantation to test the patients[30].

VI) As diagnostic test before suspicion of latent forms of myocarditis during the indeterminate stage of the disease

Together with endomyocardial biopsy, the ajmaline test is probably the most sensitive method to unmask latent forms of myocarditis during the undifferentiated or indeterminate stage[31].

b) Therapeutics:

1) Junctional tachycardias with accessory pathways (APs). When a reentrant atrioventricular tachycardia or atrial fibrillation begins, the drug (1 mg/kg m bolus followed by infusion of 15 micrograms/kg/min) or propafenone (2 mg/kg, followed by infusion of 30 micrograms/kg/min) significantly extends the effective anterograde and retrograde refractory period of AP. Both drugs are highly efficient and safe to end and prevent the reinitiation of reentrant atrioventricular tachycardia or atrial fibrillation in patients with accessory pathway (APs)[32]. This efficacy could be in part, a consequence of the capacity of inducing a prolongation of the rate-dependent nodal refractory period;
2) Through the EV via in junctional paroxysmal tachycardias, especially if there is a manifest or concealed accessory pathway included in the reentry circuit by retrograde pathway block. In these cases, it is a drug of second choice: the first ones are vagal maneuvers, adenosine and verapamil;
3) Atrial fibrillation with rate of not high ventricular response of WPW, in which there is contraindication for cardioversion: administration must be suspended if QRS duration increases above 50%;
4) Ventricular extrasystoles in bursts: "fragmentary tachycardia";
5) Sustained monomorphic ventricular tachycardia of high rate: higher percentage of success than with lidocaine: 85%.
6) In pregnant women without symptomatic ventricular ventricular tachyarrhythmias, the initial therapy should be initiated with ajmaline, procainamide or lidocaine[33].

Contraindications:

1) Cardiomegaly or important CHF;
2) Multiple valvular heart diseases;
3) Recent infarction;
4) Prolongation of preexisting QRS by branch blocks;
5) AV block;
6) Prolongation of QTc interval by potential of developing TdP that could degenerate in ventricular fibrillation[33];
7) Association with drugs of group I: strengthens the negative dromotropic effect in the His-Purkinje system;
8) β blockers and verapamil: by depressor effects in nodal conduction.
9) Brugada type 3 pattern.

Collateral effects:

They are related with the administered dose, velocity of administration, state of renal and heart function.

I) Cardiovascular

1) Low blood pressure: mild and through the EV via present in half of the cases if a dose above 50 mg administered;
2) Sinus dysfunction;
3) First-degree AV block;
4) Supraventricular tachycardia;
5) Ventricular tachycardia of the TdP type;
6) Ventricular fibrillation;
7) Prolongation of QRS by intraventricular block.

The toxicity due to an accidental excessive dose of this drug in children or suicidal people, when it exceeds 1 g, is characterized by early appearance in 1 to 2 hours and never more than 12 hours (short duration). The modifications of the ECG include: first-degree AV block (15%); intraventricular conduction defects in almost a 100%; ST-T segment alterations in 100%; extrasystoles and badly tolerated VTs. The rate of mortality by overdose is 24%, but it has not reported in diagnostic tests[34].

II) Non cardiovascular:

1) Facial heat feeling;
2) Mouth and anal burning;
3) Nausea at the time the arrhythmia disappears;
4) Transitory cholestatic jaundice (rare);
5) Agranulocytosis: it appears after 14 to 30 days, being favored by advanced age. Its origin is immunoalergic.

Medication interaction:

It must not be associated to:

1) Other class I drugs: it strengthens the negative dromotropic effect on the His-Purkinje system;
2) β blockers and verapamil: by depressor effects in nodal conduction;
3) Testosterone;
4) Estrogens;

3 and 4 because they may cause prolonged hepatic cholestasis.

Conclusions

Ajmaline was synthesized 73 years ago (1931) by Sidiqui[35], but it has not been widely spread and it is not sold in many countries. The drug is very important for the diagnosis of concealed and intermittent forms in Brugada syndrome, and it is admitted to be the ideal drug for this goal, because it provokes the repolarization modification fast, with an advantage over class IC antiarrhythmic agents (flecainide and pilsicainide) that have a strong effect on the Na^+ channel and a slow binding kinetics with this channel and a more intense negative dromotropic effect.

The pharmacological test is indicated in all the patients that suffered aborted sudden cardiac death or unexplained syncope without structural heart disease, in which ECG does not show spontaneously the typical ECG Brugada pattern

(concealed or intermittent forms) and to differentiate genuine idiopathic fibrillation from Brugada syndrome because the pharmacological test unmasks this syndrome, which is mistakenly considered idiopathic VF when concealed. It should also be conducted on the relatives of the affected patients.

The pharmacological test is indicated too in asymptomatic patients with Brugada type 3 or 2 pattern or normal ECG a non-explain family premature history on syncope or SCD in first degree relatives with < 45 years old coved type ECGs in family members.

The test with this drug in Brugada syndrome, is considered a very useful tool.

We believe that in new consensus about Brugada syndrome (Brugada Syndrome Consensus Conference), the approval of this drug by the FDA should be considered, to use it in research and diagnosis.

Other therapeutic/diagnostic purposes are being analyzed.

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