LETTERS TO THE EDITOR

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Oral loading of propafenone: restoring its role before restoring rhythm

The optimal way to convert recent onset atrial fibrillation (AF) to sinus rhythm is still a matter of interest for physicians. According to guidelines, usually the clinical strategy depends on patient's characteristics. Pharmacological cardioversion with Class I antiarrhythmic drugs is one of the main therapeutic options for restoring sinus rhythm in patients with recent onset and haemodynamically well-tolerated AF, in the absence of structural heart disease.

Stoschitzky *et al.*[1] investigated the effects of a single oral dose of 600 mg propafenone in 12 healthy males: they found that a single oral loading dose decreases heart rate, systolic blood pressure, and rate pressure product. They also observed an increased plasma concentration of propafenone during exercise and its reduction during recovery. On the basis of their observations, the Authors concluded that propafenone also exerts a β-blocking activity, and in their view, this might allow the use of oral propafenone loading also in patients with structural heart disease.

The β-blocking effect of propafenone had already been observed in previous studies, along with mild calcium channel-blocking effect, and an inhibition of potassium currents, particularly I_K.[2] The pharmacokinetics of propafenone are also complex: it undergoes extensive first-pass hepatic metabolism to 5-hydroxy-propafenone, which has a similar pharmacodynamic profile to the parent drug and contributes significantly to the therapeutic effects. Another complicating factor is that 5–10% of Caucasians (so-called 'poor oxidizers') have a reduced oxidative metabolic capacity that leads to low or even undetectable concentrations of 5-hydroxy-propafenone and high plasma concentrations of the parent drug.[3]

Even though the safety profile of a single oral loading dose of propafenone is high, there is a potential pro-arrhythmic risk: conversion of AF in atrial flutter with 1:1 atrioventricular conduction (and wide QRS) occurs in 3.5–5% of patients treated with Class 1C antiarrhythmic drugs. To prevent this undesired side effect, Marcus *et al.*[4] suggested to administer β-blockers with Class 1C antiarrhythmic drugs, since the early 90s. Moreover, the negative inotropic effect of oral propafenone may lead to transient hypotension (2.5%) and rarely pulmonary oedema (0.1%).[2,5] These complications may be even more dangerous in patients with structural heart disease, coronary artery disease, or heart failure. Furthermore, such patients are usually treated with complex drug regimens, increasing the risk of pharmacological interference and relevant clinical side effects.

Consistently with previous observations, propafenone should be avoided (even in a single oral loading dose) in elderly patients (aged >80), those with heart failure (New York Heart Association functional class >II), left ventricular dysfunction (ejection fraction <40–45%), ischaemic heart disease, systolic arterial pressure <95–100 mmHg, baseline QRS interval duration ≥0.11 s, previous evidence of second- or third-degree atrioventricular block, sick sinus syndrome, renal or liver failure, hypokalaemia, or concurrent treatment with other antiarrhythmic agents.[2,5]

In conclusion, despite the interesting findings of Stoschitzky *et al.*[1] in healthy young volunteers, we discourage the use of propafenone in patients with structural heart disease, (considering its well-documented potential negative inotropic and pro-arrhythmic effect) until larger trials are performed in such patients.

Conflict of interest: none declared.

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Cristian Martignani[1]*, Igor Diemberger[1], Matteo Ziacchi[1], Mauro Biffi[1], and Giuseppe Boriani[2]
[1]Department of Cardiovascular Medicine, S.Orsola-Malpighi Hospital, University of Bologna, Bologna, Italy
[2]Cardiovascular Division, Modena University Hospital, University of Modena and Reggio Emilia, Modena, Italy

*Corresponding author. Tel: +39 051 6363 531.
E-mail address: cristian.martignani@gmail.com

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Oral loading of propafenone: restoring its role before restoring rhythm—authors' reply

We wish to thank Martignani *et al.*[1] for their critical Letter to the Editor according to our article recently published in *Europace*[2] where they question our proposal that propafenone should not be generally excluded from cardioversion of paroxysmal atrial fibrillation in patients with structural heart disease. Recent *2016 European Society of Cardiology Guidelines for the Management of Atrial Fibrillation*[3] support the use of propafenone for acute pharmacological cardioversion in patients with new onset of atrial fibrillation. However, their restriction that propafenone should only be given to patients without structural heart disease[3] particularly bases on CAST (the *Cardiac Arrhythmias Suppression Trial*),[4] where long-term administration of flecainide and encainide, two other Class Ic antiarrhythmic agents without β-blocking effects, increased mortality when given to patients with ventricular arrhythmias and coronary artery disease.

Our data and conclusions[2] only refer to the administration of single oral doses of propafenone for cardioversion of paroxysmal atrial fibrillation. Therefore, the fact that the pharmacokinetics of propafenone may be different in different oxidisers[5] only plays a minor role since we do not recommend long-term treatment.

There is no doubt that administration of Class Ic antiarrhythmic drugs in patients with atrial fibrillation may switch to atrial flutter and that, therefore, concomitant treatment with a β-blocker or a non-dihydropyridine calcium channel blocker is recommended.[3] Therefore, it might be essential that single oral doses of 600 mg propafenone possess β-blocking effects by themselves.[2]

We fully agree that β-blockers show several side effects and contraindications such as asthma bronchiale, severe obstructive lung disease, systolic heart failure, hypotension, atrio-ventricular-blocks, and sick sinus syndrome.[1] Therefore, even single oral doses of propafenone should be given carefully to patients with these diseases.