Flecainide in the treatment of ventricular and supraventricular arrhythmias

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Document Version
Publisher's PDF, also known as Version of record

Publication date:
1988

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):
Chapter 1 gives an overview on the development and application of antiarrhythmic drugs in general and the classification of antiarrhythmic drugs. The development of flecainide acetate, a “fluorine-for-hydrogen substitution” derivative of procainamide, started in 1966. The most important pharmacokinetic properties are its good absorption without significant first pass effect by the liver, its metabolism (dealkylation) by the liver and inactivation of metabolites by glucuronidation and their excretion by the kidneys. Plasma half-lives range from 7 to 22 hours and are prolonged in elderly subjects with frequent ventricular premature beats, congestive heart failure and impaired renal function. The electrophysiological investigations showed dose related prolongation of QRS duration, HV-, AH- and PR interval. Refractory periods were less influenced. Especially in patients with AV node dysfunction flecainide should be carefully administered. In contrast, patients with sinus node dysfunction seem to be influenced to a lesser degree.

The second chapter deals with the value of flecainide acetate in supraventricular tachycardias as reported in the literature together with parts of our finding. Flecainide acetate in a dose of 2mg/kg is highly efficacious in the termination of recent-onset atrial fibrillation (up to 90%), atrial tachycardias (92%) and AV reentry tachycardias (90%). However, the efficacy in the termination of atrial flutter is poor. Efficacy during long-term therapy of supraventricular arrhythmias with flecainide acetate is also satisfactory.

In chapter 3 a review on the efficacy of flecainide acetate in ventricular arrhythmias is presented. Flecainide acetate was demonstrated to be very effective in suppression of premature ventricular beats, couplets and nonsustained ventricular tachycardias. However, the treatment of sustained ventricular tachycardias and fibrillation is often disappointing, although the efficacy of flecainide was not shown to be inferior to that of amiodarone, which is generally considered to be the most effective drug in these circumstances. Also a review of proarrhythmic effects is presented in this chapter.

In chapter 4 we describe 9 patients with congestive heart failure class III according to the NYHA. The patients could be divided in 2 groups in terms of their pharmacokinetic and haemodynamic properties. The first group of 5 patients showed a relatively short
plasma half-life, normal plasma clearance, normal renal function, normal or slightly enlarged left atrium and left ventricle. In contrast, the second group showed prolonged plasma half-life, low plasma clearance, impaired renal function, enlarged left atrium and ventricle. Although maximum plasma levels were low in the second group, the antiarrhythmic efficacy was even better compared to the first group. We presume that a different relation between plasma and tissue levels of flecainide acetate caused this good antiarrhythmic efficacy. Furthermore, after an initial decrease of plasma levels a second maximum was found about 2 to 3 hours after the infusion. We presume that reabsorption as a consequence of enterohepatic recirculation may lead to a second rise of plasma levels, especially in patients with impaired renal and cardiac function in whom liver excretion and metabolisation become increasingly important.

In chapter 5 we describe the acute conversion of recent onset and chronic atrial fibrillation with oral versus iv administered flecainide acetate. In recent onset atrial fibrillation both regimens had a comparable efficacy (71% and 77% respectively). The only difference between the 2 regimens was the mean time to conversion (as may be expected), eg 104 minutes after oral and 14 minutes after starting the iv administration of flecainide. Chronic atrial fibrillation could not be converted by any of these regimens.

In chapter 6 we compare the efficacy of flecainide 100 mg b.i.d. to quinidine 500 mg b.i.d. in 26 patients with paroxysmal atrial fibrillation. An almost maximal effect was obtained with flecainide in a dosage of 100 mg twice daily (46% of the patients showed complete abolition of tachycardias). An increase of the dosage to 100 mg t.i.d. resulted in a large number of side effects whereas efficacy was almost unchanged. On quinidine therapy the efficacy on the first regimen of 500 mg b.i.d. was significantly lower compared to flecainide 100 mg twice daily (17% only). A comparable efficacy could be reached by increasing the dosage of quinidine from 500 mg b.i.d. to 750 mg b.i.d. (35% of the patients no longer showed tachycardias). However, the number of side effects was much higher during treatment with quinidine, with the same efficacy as far as prevention of paroxysms of atrial fibrillation is concerned.

In chapter 7 we describe the efficacy of iv flecainide acetate in 2 patients with recent onset atrial fibrillation and rapid ventricular response in the setting of a Wolff-Parkinson-White syndrome. Both patients had a short antegrade refractory period of the accessory pathway, the shortest RR-interval were 180 and 190 msec. Atrial fibrillation was terminated in both patients after slowing of the ventricular rate and regularisation of the atrial activity.

In chapter 8 the efficacy of flecainide acetate in the long term treatment of supraventricular tachycardias in 20 patients was described. Furthermore, the value of pro-
Flecainide 6 patients no longer had inducible tachycardias. None of the patients with a Wolff-Parkinson-White syndrome showed atrial fibrillation after flecainide. During a mean follow-up period of 11 months, 65% of the patients had no recurrence. Positive and negative predictive value of the electrophysiological investigation was 50 and 100%, respectively. Patients with a Wolff-Parkinson-White syndrome, especially younger patients, prefer more and more surgical intervention even when medical treatment is successful.

In chapter 9 the results of flecainide in the treatment of sustained ventricular tachycardia or ventricular fibrillation are presented. In 37 patients the aetiology of the tachyarrhythmia was coronary artery disease and in 13 patients other aetiologies (cardiomyopathy, valvular disease or idiopathic). During a 4 week in hospital period therapy failed in 8 patients with coronary artery disease. In 6 patients recurrence of tachycardias developed (including proarrhythmic effects) and in 2 patients side effects necessitated discontinuation of flecainide. Thirty-eight patients completed a follow-up period of 1 year with an overall success rate based on intention to treat of 54%. Patients with tachyarrhythmias based on coronary artery disease had a significantly lower ejection fraction (31% versus 47%) and earlier recurrences (7.5 weeks versus 20 weeks) compared to the patients with tachyarrhythmias based on other aetiologies. Therefore, calculated after 4 weeks hospitalisation patients with tachyarrhythmias based on coronary artery disease showed a higher success rate compared to patients with arrhythmias based on other aetiologies (78% versus 55%). Failures in the group with arrhythmias based on coronary artery disease had a significantly lower ejection fraction. Programmed electrical stimulation (N = 28) showed a positive and negative predictive value of 40%. Holter monitoring (N = 24) showed a positive and negative predictive value of 70 and 86% respectively. Since exercise testing (N = 30) showed arrhythmias only in 20% of the patients the number is too small for a reliable conclusion.

In conclusion, we have established that flecainide is a valuable drug in the treatment of almost all cardiac arrhythmias except atrial flutter. Efficacy in termination of recent onset-atrial fibrillation, atrial tachycardias and AV-reentry tachycardias has been proven beyond any doubt. It may even be preferred over quinidine in terms of efficacy and toxicity, in the prevention of paroxysms of atrial fibrillation. Furthermore, we have shown that flecainide is very effective in the long-term treatment of sustained ventricular and supraventricular tachycardias, including atrial fibrillation in the setting of the Wolff-Parkinson-White syndrome. However, care should be taken in starting flecainide or in adjustment of the dose, especially in patients with coronary artery disease and impaired left ventricular function.