Drug Development and Evaluation

8

Flecainid

Experimentelle Befunde und klinische Erfahrungen

Herausgegeben von
F. Bender und G. Cronheim

Gustav Fischer Verlag · Stuttgart · New York

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Flecainid-Symposium in Mainz am 9. Januar 1982

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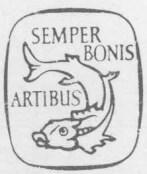
128 Abbildungen und 30 Tabellen



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Flecainid ist die internationale Kurzbezeichnung
(International Nonproprietary Name INN) für N-(2-Piperidylmethyl)-2,5-bis-(2,2,2-trifluorethoxy)-benzamidacetat = Flecainidacetat
Die Substanz ist in der Literatur auch als R-818 bezeichnet worden.
Flecainid wird in Deutschland unter dem Namen TAMBOCOR® von Kettelhack Riker Pharma GmbH, 4280 Borken, vertrieben.

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Vorwort

Trotz zweifellos bedeutender Fortschritte in der Therapie der Arrhythmien während der letzten Jahre läßt die Behandlung dieser oft lebensbedrohenden Störungen noch viele Wünsche offen. Die in diesem Symposiums-Buch beschriebenen Erfolge berechtigen zu der Hoffnung, daß mit dem neuen Antiarrhythmikum Flecainid eine Substanz zur günstigen Beeinflussung eines weiten Spektrums von Arrhythmien zur Verfügung steht.
Pharmakologische und elektrophysiologische Befunde wie auch zahlreiche klinische Beobachtungen werden dargestellt und diskutiert. Flecainid unterscheidet sich in einer Reihe pharmakokinetischer und pharmakodynamischer Besonderheiten von den anderen Substanzen der Klasse I.
Selbstverständlich gibt es noch sehr viele unbeantwortete Fragen, deren Beantwortung noch Jahre intensiver Forschung in Anspruch nehmen wird. Die ersten klinischen Erfahrungen liegen bereits 7 Jahre zurück. Die bisherigen Erprobungen durch viele Arbeitsgruppen ergeben, daß ein weitgehender Einsatz von Flecainid in der Behandlung von Arrhythmien empfohlen werden kann. Natürlich verbleibt noch viel Raum für weitere wissenschaftliche Untersuchungen.

Ohne die Hilfe vieler Mitarbeiter wäre das Symposium und dieser Symposiumsband sicher nicht so gut gelungen. Unser besonderer Dank gebührt Frau U. Hoffmann in Borken, die verwaltungstechnisch die Hauptlast der Vorarbeiten und der Durchführung der Tagung übernommen hatte.

April 1982

F. Bender
G. Cronheim

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English Summaries

Pharmacological and electrophysiological effects of flecainide

U. Borchard, C. Hirth and J. J. Schulze

The effects of flecainide on electrophysiological parameters and force of contraction were investigated in guinea-pig, rabbit as well as human heart preparations.
Flecainide (up to 10 µmol/l) increases the action potential duration at 30 and 90 % repolarization and the functional refractory period in guinea-pig papillary muscle. At 30 µmol/l, it shortens the action potential and decreases the plateau height without significant change in resting potential. Correspondingly, a negative inotropic effect in atrial and ventricular preparations is observed only at flecainide concentrations higher than 10 µmol/l. This minor negative inotropic effect results in a small depression of $\dot{V}_{max}$ in »slow response« papillary muscle action potentials.
Flecainide predominantly reduces the maximal upstroke velocity ($\dot{V}_{max}$) of the fast action potential upstroke in a use-dependent manner. With increasing stimulation frequency, an increase of $\dot{V}_{max}$ suppression is observed. Flecainide delays recovery from inactivation of the fast sodium channels.
The potential dependent action of flecainide on $\dot{V}_{max}$ is demonstrated by a shift to more negative potentials of the membrane-responsiveness-curve and of the curve relating $\dot{V}_{max}$ to the potential of the K^+-depolarized membrane (h_∞-curve).
The effects of flecainide on action potentials of sinus node cells are only present at concentrations higher than 10 µmol/l, which lead to a decrease in spontaneous frequency and an increase in action potential duration. Similar results are obtained in A-V nodal cells.
When comparing the electrophysiological effects of flecainide with those of other antiarrhythmic drugs, it is apparent that flecainide possesses lidocaine – as well as quinidine – like characteristics and therefore represents a separate, unique Vaughan-Williams Class I antiarrhythmic drug.

Hemodynamics and stimulation thresholds to atrial and ventricular repetitive extrasystoles and fibrillation in the non-ischemic dog myocardium in the presence of flecainide

H. Gülker, J. Thale, H. Heuer, U. Weiß and F. Bender

Flecainide has a dose-dependent antifibrillatory action on non-ischemic dog myocardium in situ. This effect is similar in atrial and ventricular tissues. The predominant antiarrhythmic mechanism seems to be represented by suppressing reentry phenomena depending on »depressed fast response« mechanisms. The antifibrillatory action of flecainide is more powerful than that of the same dose of lidocaine. This difference accounts for the antiarrhythmic efficacy of flecainide in lidocaine resistant arrhythmias.
Changes in myocardial vulnerability in the presence of flecainide can be determined by measuring the electrical fibrillation threshold, but not by evaluating the threshold of repetitive extrasystoles. Thus, the »Repetitive Extrasystole Threshold« seems to be of only minor importance for the evaluation of the antifibrillatory efficacy of antiarrhythmic drugs.

Hemodynamic changes induced by therapeutic flecainide concentrations are minor. A slight decrease of contractility is observed.

Influence of flecainide on hemodynamics and experimentally induced early and late arrhythmias following acute infarction

J. Thale, H. Gülker, B. Brisse, H. Heuer and F. Bender

This study covered the effect of flecainide in two different phases of infarction in dogs occurring after coronary occlusion: An early phase in the first 30 minutes after occlusion and a second phase 6 – 24 hrs after occlusion.
Flecainide (bolus 2 mg/kg followed by 50 mcg/kg/min) has no antifibrillatory effect in the first minutes after coronary occlusion. Six to 24 hrs after coronary occlusion flecainide reduces ventricular arrhythmias by 80 to 90 % (salvos, tachycardias, and R on T phenomena). In contrast, lidocaine (bolus 2 mg/kg followed by 100 mcg/kg × minute) shows no significant effect.
In the second infarction phase hemodynamics, contractility and O_2-consumption are not influenced by the highest flecainide dose (2mg/kg i.v. followed by 200 mcg/kg × minute), except that an increase in frequency occurs.
The results suggest that flecainide is a promising agent in the treatment of lidocaine refractory arrhythmias.

Effects of flecainide on hemodynamic parameters in normal volunteers and patients with heart disease

M. Hodges

The hemodynamic properties of flecainide have been studied in 10 normal volunteers and in 20 patients with congestive heart failure (New York Heart Association Class II). This was a single dose, double-blind crossover comparison of flecainide (250 mg), and placebo. The hemodynamic parameters were determined from M-mode echocardiography and standard one minute electrocardiography. The measurements were evaluated by a two-way analysis of variance.
The results indicated small but significant increases in heart rate, the pre-ejection period and in the PEP: LVET ratio which is considered the most sensitive index of left ventricular contractility. Decreases were noted in ejection fraction, and the velocity of contractile fiber shortening. No changes were noted in blood pressure or left ventricular ejection time.
The PR interval, QRS complex and QTc interval were lengthened. It is important to note that the QTc increase was due exclusively to the widening of the QRS complex, and that the JT interval was not prolonged.

Metabolic disposition of flecainide acetate in man

G. J. Conard

The plasma half-life of unchanged flecainide is relatively long in healthy, male subjects and in patients with premature ventricular contractions (PVCs). Following single intravenous or oral doses to subjects, the plasma half-life was found to range from 7 to 22 hours (mean, 13 hours); after multiple oral dosage, the half-life is only somewhat longer (mean, 16 hours) in subjects. With multiple dosage, flecainide predictably accumulates in plasma based on its long half-life. For patients with PVCs following multiple oral dosage, the plasma half-life was found to range from 12 to 30 hours (mean, 20 hours) and is longer than that for healthy subjects; this may be a result of older age, multiple dosage, cardiovascular status or other factors. In addition, plasma half-life is apparently independent of dose. Based on plasma pharmacokinetics, flecainide should be suitable for twice daily dosage in most patients for chronic treatment of arrhythmias; efficacy data confirm this.

Following oral dosage (capsule or tablet), the absorption of flecainide is reasonably prompt and essentially complete in humans. Peak plasma levels of drug are attained at 2 to 4 hours, on an average, after a single oral dose. On an average, 95 % of an oral dose is absorbed into the systemic circulation as unchanged drug; thus, flecainide does not undergo any extensive presystemic biotransformation during absorption or on the first pass through the liver. After single and multiple oral doses, plasma levels are linearly related to dose. Thus, oral dosage provides prompt and predictable plasma levels of flecainide.

After a single oral dose, a substantial amount of unchanged flecainide (mean, about 25 % of the dose) is excreted in human urine; renal clearance of flecainide averages about 170 ml/min. In addition, flecainide undergoes extensive biotransformation and its metabolites are mostly excreted in human urine. One urinary metabolite (meta-o-dealkylated flecainide) has been identified; this metabolite (free and conjugates) accounts for about 20 % of the dose. This o-dealkylated metabolite has some detectable, but low level of antiarrhythmic activity. Thin layer chromatography separations show that only 3 other metabolite fractions are present in human urine and that all human metabolite fractions are present in dog and rat urine. Thus, from a metabolism viewpoint, the chronic evaluation of drug toxicity in these animal species is a reasonable assessment of flecainide safety for humans.

Moderate renal failure has no apparent influence on the rate of unchanged flecainide elimination from plasma while endstage renal disease may increase the plasma half-life of flecainide in some patients. Hemodialysis removes only a small amount of unchanged flecainide (mean, 1.0 % of the dose). Since drug elimination may be slower in some patients with more severe renal disease and since metabolites may accumulate in plasma, dosage should be adjusted down (25 to 50 %) for patients with creatinine clearance of 20 ml/min/m^2 or less.

In vitro results indicate that flecainide is not extensively bound to human plasma proteins (mean, about 40 % bound); also, the extent of binding is independent of plasma drug level over a wide range (15 to about 3400 ng/ml) that includes and markedly exceeds therapeutic levels. Thus, consequential interactions with other drugs on protein binding would not be expected.

During efficacy studies in patients with PVCs, minimum therapeutic plasma levels of flecainide (associated with 90 % or greater suppression of PVCs) were found to range from about 200 to 1000 ng/ml (mean, about 500 ng/ml); these levels and trough plasma levels up to about 1600 ng/ml are well tolerated (no consequential adverse effects).

Spontaneous variability of tachycardic ventricular arrhythmias

D. Andresen, E.-R. v. Leitner, K. Wegschneider, U. Tietze and R. Schröder

The spontaneous variability of tachycardic ventricular arrhythmias was evaluated on the basis of three consecutive 24-hour electrocardiographic recordings from each of 42 patients. It is concluded that the use of an analysis of variance is not the best procedure to establish the efficacy of an antiarrhythmic drug since this method overestimates the spontaneous variability in a given patient. A regression analysis represents a more suitable method to determine antiarrhythmic efficacy for both simple and complex forms of arrhythmias.
Utilizing 24-hour ECG recordings, a 75 % reduction of ventricular extrasystoles from a baseline of more than 30 VES/hour is required to establish the anti-arrhythmic efficacy of a drug. In the case of ventricular pairs of 10 or more per day, a 90 % reduction would be necessary to be sure of measuring a drug effect rather than spontaneous variability.

Effects of flecainide on sinus node function and antegrade conduction

L. Seipel, G. Breithardt and R. R. Abendroth

The electrophysiological effect of the new antiarrhythmic drug flecainide (R-818) was tested in 27 patients with and without disturbances of sinus node function and intraventricular conduction. Flecainide was given intravenously in a dose of 1 mg/kg and 2 mg/kg. Constant »therapeutic« plasma levels were reached by application of 1 mg/kg as a bolus and an additional infusion of 1 mg/kg during the test period of 20 min.
The drug had no significant effects on sinus node function even in patients with sinus node dysfunction tested so far. Intracardiac conduction time was prolonged within all compartments of the heart in a dose-dependent manner. After bolus injection of 1 mg/kg, the HRA-A interval lengthened by 10.4 %, the A-H interval by 13.5 %, the H-V time by 15.7 % and the V-RVA interval by 29.1 % of the control value. In addition, the QRS complex widened by 8.1 %. After 2 mg/kg flecainide the HRA-A interval was prolonged by 9.0 %, the A-H interval by 24.4 %, the H-V time by 40.2 %, and the V-RVA interval by 16.5 % of the control value. The QRS complex widened by 24.2 %. In contrast, there was only a small and often insignificant increase in the refractoriness of the different compartments of the heart (5–15 % increase of the control value). In two patients with bundle branch block, a higher degree A-V block distal to the H potential occurred after 2 mg/kg flecainide. These electrophysiological effects may explain some antiarrhythmic actions of flecainide. In addition, possible side effects of the drug can be assessed. In patients with intra-ventricular conduction defects, the drug should be used with caution, especially when given i.v. in higher doses.

Effects of flecainide on electrophysiological parameters of the right ventricle and the His-Purkinje-System

T. Pop, T. Meinertz, N. Treese, W. Kasper and C. J. Kang

In 10 patients the effects of flecainide (2 mg/kg i.v.) on electrophysiological parameters were analyzed. Flecainide significantly prolongs the QRS-duration, the HV-interval, the effective refractory period of the right ventricle and the relative refractory period of the His-Purkinje-System. Pre-existing intra-His-reentry is inhibited (3 patients) or partially inhibited (2 patients) by flecainide. The critical S_2H_2 interval and the inner and outer limit of the echozone is increased. The results resemble those of other Class I A antiarrhythmic drugs. The demonstrated depressive effect of flecainide on the ventricular myocardium and Purkinje-fibers possibly explains the good suppression of ventricular arrhythmias by flecainide.

Effects of flecainide on induced supraventricular reentry tachycardia

H. Neuss, J. Buss, M. Schlepper, V. Mitrović, R. Berthold and W. A. Musial

Electrophysiological parameters were analyzed in 27 patients with therapy-refractory paroxysmal supraventricular tachycardia before and after flecainide (100 mg i.v. in 5 min).
Flecainide significantly slows conduction time in the atrium, AV-node, and His-Purkinje-System. The QRS-complex and the functional effective refractory periods of the AV-node and atrium are prolonged. WPW-syndroms are suppressed mainly by depressing accessory VA-conduction.
Flecainide suppresses AV-node reentry arrhythmias primarily by slowing conduction in the retrograde pathway, although a prolongation of AH-interval counteracts this mechanism.
Long term studies have shown that flecainide is an important therapeutic alternative in the treatment of paroxysmal supraventricular tachycardia.

Effects of flecainide on induction of ventricular tachycardia

G. Breithardt, M. Borggrefe, H. L. Yeh and L. Seipel

Thirteen patients (54 ± 11.8 years) with either spontaneously occurring ventricular tachycardia ($n = 12$) or recurrent syncope ($n = 1$) probably due to ventricular tachycardia were studied electrophysiologically. In all patients, ventricular tachycardia could be initiated by programmed right ventricular stimulation during the control study.
After several days of oral administration of flecainide (400 to 500 mg per day), sustained ventricular tachycardia could still be initiated in seven cases that had to be interrupted by overdrive stimulation in five cases, and by cardioversion in the remaining two. In six cases short, self-terminating episodes of ventricular tachycardia were induced. In four patients, no change in the mode of induction of ventricular tachycardia was observed, whereas in seven cases ventricular tachycardia was more difficult to induce (i. e. later during the step-like stimulation program). The mean

rate of induced ventricular tachycardia decreased from 215 ± 59.4/min (± S. D.) to 169 ± 44.1/min during flecainide.
Thus, flecainide exerts a marked effect on the rate of induced ventricular tachycardia, whereas the mode of induction did not change considerably. The prophylactic effect of long-term therapy with flecainide in patients with recurrent ventricular tachycardia has still to be demonstrated.

Refractory period changes of ventricular extrasystoles induced by flecainide

D. W. Fleischmann and K.-D. Grosser

The effect of flecainide (1.5 mg/kg i.v.) on sinus-rhythm, blood pressure, and ventricular refractory periods was investigated in 16 patients. The effective ventricular refractory period was determined during constant atrial pacing at 80 and 100 impulses/minute.
The intravenous injection of flecainide has no significant effect on blood pressure and sinus rhythm. The refractory period of the ventricle during constant pacing is not changed, while the effective refractory period of early extrasystoles (initiated 30 msec after the effective refractory period at normal pacing) was significantly prolonged. In contrast, control measurements show a shortening of the refractory period of the extrasystoles. Thus, in the presence of flecainide, refractory periods of the basic rhythm and the extrasystoles show adaption, a mechanism which possibly reduces the development of ventricular reentry extrasystoles or tachycardia.

Clinical observations after intravenous injection of flecainide

F. Bender

Flecainide has been given by i.v.-injection to 40 patients with mostly ventricular extrasystoles, but including also a few other forms of cardiac arrhythmias. Since these were the first clinical tests with this new drug, we selected initially patients with relatively frequent and stable ventricular extrasystoles but without any complicating diseases. Subsequently, this restriction was abandoned. All patients had been therapy resistant to at least two antiarrhythmic drugs.
An i.v. dose of 1 – 2 mg/kg given within 1–2 minutes suppressed or eliminated the arrhythmias within a few minutes, frequently before the full dose was administered. The antiarrhythmic effect lasted in most patients for several hours.
The suppression of extrasystoles was good (> 80 %) or very good (100 %) in about 65 % of the cases. In two patients with therapy resistant ventricular tachycardia, the injection of flecainide produced a normal sinus rhythm. Good results were also obtained in 7 cases of chronic supraventricular extrasystoles. In two cases with WPW-syndrome, the antegrade paranodal pathway was blocked by flecainide.
Side-effects which are apparently dose-dependent, were always mild or moderate and included dizziness, visual disturbances, pressure in the head and paresthesia in the mouth. Serious adverse reactions were never observed.

Oral use of flecainide compared to placebo tablets

W. Steinbrunn and H. Mattmann

Flecainide was compared to placebo tablets in the treatment of complex ventricular tachyarrhythmias in 8 patients. The frequency of the premature ventricular beats was determined from 24-hour ECG recordings, obtained twice during the placebo (pre-drug), flecainide and post-drug period. Flecainide was given at a dose of 200 mg (2 tablets) b. i. d. While no effect on the frequency of premature ventricular beats was observed after the placebo tablets, flecainide produced complete or almost complete ($> 90\%$) suppression in 6 patients. In the remaining two patients, the suppression reached about 70 %. Side-effects in form of dizziness, fatigue and paresthesia in the mouth were reported by 1 patient.

Results of long-term use of flecainide in patients with therapy refractory stable chronic ventricular extrasystoles, including the results of blood level determinations

H. U. Bramann, B. Brisse, H. Kuhs and F. Bender

Twelve patients with stable chronic ventricular extrasystoles were treated for at least 12 months and in some cases up to 24 months with oral flecainide at an average daily dose of 300 mg. All patients had been resistant to at least three and in some cases seven marketed anti-arrhythmic drugs. The response to flecainide was good in 7 patients with an average reduction of ventricular extrasystoles of 60–90 %, observed on repeated long-term ECG recordings taken during the treatment.

In 4 patients, the reduction was 40–60 % and in 1 patient it averaged 25 %, but was still better than what had been achieved with other drugs. All patients showed an improvement in their Lown Classification.

Flecainide was well tolerated in this group of patients. Side-effects in form of minor visual disturbances and dizziness were reported by 3 patients and disappeared spontaneously after a few days. In a fourth patient, the side-effects were more pronounced, but disappeared after reducing the dose from 400 to 300 mg/day.

Results of repeated hematological and biochemical tests did not indicate any abnormalities or signs of organ toxicity. Ophthalmological examinations after about 3 months of therapy did not reveal any drug induced changes.

Plasma levels showed the expected direct correlation with dose and low intra-patient, but high inter-patient variability. A correlation between plasma levels and suppression of ventricular extrasystoles could not be established in this group of patients.

In some patients, the PR interval and the QRS complex were lengthened by about 10 %. In only one case with a high plasma level of 1300 ng/ml was a greater QRS widening to 0.14 sec observed.