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Cardiac electrophysiological effects of falipamil in the conscious dog: comparison with alinidine

Michel Boucher [a,b,*], Claude Chassaing [a], Eric Chapuy [a,1]

[a] *INSERM U.195, Faculty of Medicine, Clermont-Ferrand, France*
[b] *Department of Physiology, Faculty of Pharmacy, Clermont-Ferrand, France*

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Abstract

We studied the cardiac electrophysiological effects of falipamil, a specific bradycardic agent, in conscious dogs, in comparison with those of alinidine. Sinus rate, corrected sinus recovery time, and Wenckebach point were measured in six intact dogs. Atrial rate, ventricular rate, and atrial effective refractory period were measured in six atrioventricular-blocked dogs. In both groups, blood pressure was also monitored. Each dog received, with at least a three-day interval, falipamil (hydrochloride) and alinidine (hydrobromide) in four successive intravenous injections, 30 min apart, at 0.5, 0.5, 1, and 2 mg kg^{-1}. Falipamil increased sinus rate and atrial rate, but decreased ventricular rate, whereas alinidine decreased sinus rate and ventricular rate, but increased atrial rate. Falipamil shortened corrected sinus recovery time and increased Wenckebach point, whereas alinidine lengthened corrected sinus recovery time and decreased Wenckebach point. Falipamil and alinidine increased atrial effective refractory period. Neither falipamil nor alinidine modified mean blood pressure in either group. Overall, these results show that (a) falipamil exhibits effects on the electrical activity of the heart, reflecting the predominant direct vagolytic effect of this drug, (b) alinidine exhibits effects reflecting the marked antiarrhythmic potential of this agent, and (c) thus indicate that two drugs with almost identical specific bradycardic properties can produce quite different electrophysiological effects in the conscious dog.

Keywords: Falipamil; Alinidine; Sinoatrial node; His bundle; Atrial myocardium; AV node; Blood pressure; (Conscious intact dog); (AV-blocked dog)

1. Introduction

Falipamil, (5,6-dimethoxy-2-{3-[(alpha-(3,4-dimethoxy) phenylethyl) methyl-amino] propyl}-phthalimidine), is a verapamil derivative that has been reported to decrease the sinus rate almost exclusively, when given at low concentrations, and thus is known as a specific bradycardic agent (Dämmgen et al., 1981; Kobinger and Lillie, 1981; Lillie and Kobinger, 1983). This bradycardic effect results from a reduction in the diastolic depolarization rate and a prolongation of the action potential duration. Blockade of the slow inward calcium current (i_{si}) (Osterrieder et al., 1981; Trautwein et al., 1981; Pelzer et al., 1982; Trautwein et al., 1983), the mixed sodium potassium inward pacemaker current (i_f) (Van Bogaert and Goethals, 1987; Brunner and Kukovetz, 1988), and the delayed rectifier outward current (i_k) (Osterrieder et al., 1981; Trautwein et al., 1981; BoSmith et al., 1993) has been suggested to explain these effects. However, a number of electrophysiological results reported for falipamil are controversial. This agent has been reported to decrease maximal atrial driving frequency (Kobinger and Lillie, 1981), i.e., prolong atrial effective refractory period, to increase atrioventricular (AV) nodal conduction time (Kawada et al., 1984) and A-H interval (Takeda et al., 1989), to increase conduction time of the His-Purkinje-ventricular system (Kawada et al., 1984) or not to modify H-V interval (Takeda et al., 1989) and QRS (Kobinger and Lillie, 1981), and to increase AV conduction time (Takeda et al., 1989) or not to modify P-Q interval (Kobinger and Lillie, 1981). Falipamil has also been reported to increase action potential duration at 50%, 80% and 90% repolarization (Trautwein et al., 1981; Hohnloser et al., 1982; Pelzer et al., 1982) or, without more precise information, to increase action potential duration (Osterrieder et al., 1981). All these studies have been performed either in vitro or in anaesthetized animals. Under such experimental conditions, various factors can

* Corresponding author. Department of Physiology, Faculty of Pharmacy, F-63001 Clermont-Ferrand Cedex 1, France. Fax: +33.73.277907.

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interfere with results, particularly the supporting media and type of anaesthesia. These factors, along with the range of doses used and the diversity of parameters used to assess one single function such as AV conduction, may account for the discrepant results obtained. In addition, in conscious dogs, the direct vagolytic action of falipamil (Kobinger and Lillie, 1981; Osterrieder et al., 1981) can interfere with its true effects (Boucher et al., 1994). This interference, which was more or less severe according to the anaesthetic used in the reported in vivo studies, may also partly account for the results observed.

To our knowledge, no electrophysiological study of falipamil had been performed hitherto in conscious animals. Therefore, we studied the effects of falipamil on sinoatrial node and His bundle automaticities, atrial myocardium and AV node refractoriness, and blood pressure as a function of dose in conscious dogs. These effects were compared with those of alinidine, another specific bradycardic agent that has already been shown to affect cardiac electrophysiological parameters (Boucher et al., 1995).

2. Materials and methods

Twelve mongrel dogs of either sex weighing 15–22 kg were used in this study. They were housed in individual cages in a large colony room, with food and water continuously available in their cages. The study conformed to the NIH *Guidelines for Care and Use of Laboratory Animals.*

2.1. Surgical preparation and instrumentation

In six dogs (intact dogs) out of the 12, two wired stainless steel electrodes were implanted, under sodium pentobarbital anaesthesia and aseptic conditions, 1.5 cm apart on the external surface of the right atrium near the sinoatrial node, and the leads were exteriorized through the neck. Three of these dogs were in addition fitted with a catheter for long-term measurement of blood pressure; the catheter was inserted into the left omocervical artery and connected to a valve fixed on the neck. In the other six dogs (AV-blocked dogs), AV block was induced by crushing the His bundle with forceps introduced through the open right atrium during temporary occlusion of the venae cavae [modified Fredericq's technique (Boucher and Duchêne-Marullaz, 1985)]. Two atrial surgical electrodes (in all six dogs) and an arterial catheter (in three dogs) were implanted as described. All dogs were left to recover for at least eight to ten days before experiments were performed.

2.2. Measurements

Electrocardiographic and blood pressure monitoring were carried out with a Cardiopan III T instrument (Massiot-Philips) and a Statham P23 Gb transducer connected to the arterial valve and linked to the recorder through a pressure module. Corrected sinus recovery time and Wenckebach point were measured in intact dogs. Corrected sinus recovery time was measured according to the method described previously for humans by Mandel et al. (1971). Corrected sinus recovery time, which corresponds to the postoverdrive pacing pause, was determined as the difference between the measured pause and the mean resting sinus cycle length. Atrial pacing was applied for 1 min using 2-ms rectangular pulses from a Hugo Sachs Electronik 6512 stimulator; the stimulation voltage was 1.5 times the threshold voltage and pacing frequency was twice the spontaneous sinus rate. Wenckebach point was determined by carrying out atrial pacing (2-ms rectangular pulses – 1.5 times threshold voltage), the frequency of which was gradually increased from the spontaneous sinus rate until type I second-degree AV block occurred. Atrial effective refractory period was measured in AV-blocked dogs by the extrastimulus method involving single premature atrial stimuli. Atrial pacing was applied in 2-ms rectangular pulses from a Janssen programmable stimulator; the stimulation voltage was 1.5 times threshold voltage and pacing frequency was twice the spontaneous atrial rate observed before the first injection. Single premature atrial stimuli were brought closer to the preceding stimulus in 5-ms steps at every eighth pacing stimuli. During recording, the previously trained dogs were placed on a table and lightly restrained. One microcatheter was fitted in a cephalic vein before each test to allow painless drug administration.

2.3. Protocol

Falipamil (hydrochloride) and alinidine (hydrobromide) were administered at doses of 0.5, 0.5, 1, and 2 mg kg^{-1}. The study design was the same in all cases. Each dog received the four successive intravenous (i.v.) injections, lasting 30 s each, of each drug, 30 min apart. The experiments were carried out at least eight to ten days postoperatively, by which time the dogs were thoroughly familiarized with the experimental conditions. At least 72 h elapsed between each drug evaluation in the same dog; evaluations were done in random order. Sinus rate (determined for 30 s), corrected sinus recovery time, Wenckebach point, and mean blood pressure were measured in intact dogs before the first injection and for 30 min after each injection. Atrial rate (so called to differentiate it from sinus rate in intact dogs), ventricular rate, atrial effective refractory period, and mean blood pressure were measured in AV-blocked dogs, also before the first injection and for 30 min after each injection. As previously shown in our laboratory, all these parameters remain highly stable throughout the experiments (Duchêne-Marullaz et al., 1982; Dubray et al., 1983; Kantelip et al., 1988).

2.4. Drugs

Falipamil (hydrochloride) and alinidine (hydrobromide) were supplied by Boehringer Ingelheim Laboratories (Reims, France). Drugs were dissolved in physiological saline and doses are expressed in terms of the salt.

2.5. Statistical analysis

Results were expressed as arithmetic means ± S.E.M. and also as mean maximal variations ± S.E.M. The latter parameter was calculated from the maximal or minimal value attained during the 30 min following each injection. The mean difference between individual values and their corresponding basal values was calculated, yielding mean maximal variations ± S.E.M. The effects of each drug on the different parameters were established by analysis of variance in complete blocks without repeated measures, followed, when the F value was significant, by multiple comparisons by Dunnett's test.

3. Results

3.1. Effects on sinoatrial node automaticity

3.1.1. Sinus rate

In intact dogs, falipamil increased the sinus rate from the third dose onward ($P < 0.01$) (Fig. 1). This tachycardic effect, which appeared immediately after injection, increased with dose, lasting 25 min and reaching 27% at the highest cumulative dose of 4 mg kg^{-1}. In contrast, alinidine decreased the sinus rate from the first dose onward ($P < 0.001$) (Fig. 1). This bradycardic effect appeared immediately after injection, lasted ≥ 30 min and reached 43% at the highest dose.

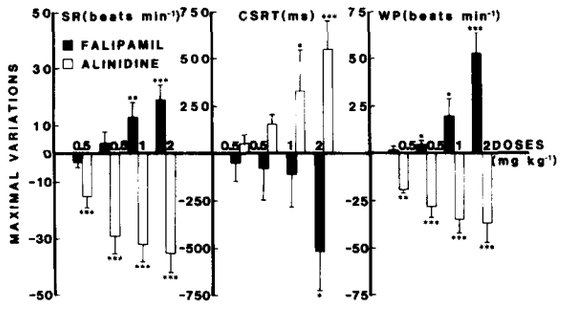

Fig. 1. Maximal effects on sinus rate (SR), corrected sinus recovery time (CSRT), and Wenckebach point (WP) after four successive intravenous injections of 0.5, 0.5, 1, and 2 mg kg^{-1} falipamil hydrochloride (solid columns) and of the same doses of alinidine hydrobromide (open columns) in conscious intact dogs. Values are means for groups of six dogs. Vertical lines show S.E.M. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$ in comparison with corresponding control values (71 ± 4 and 81 ± 9 beats min^{-1} for SR; 1004 ± 176 and 770 ± 86 ms for CSRT; 85 ± 12 and 105 ± 9 beats min^{-1} for WP, before falipamil and alinidine, respectively).

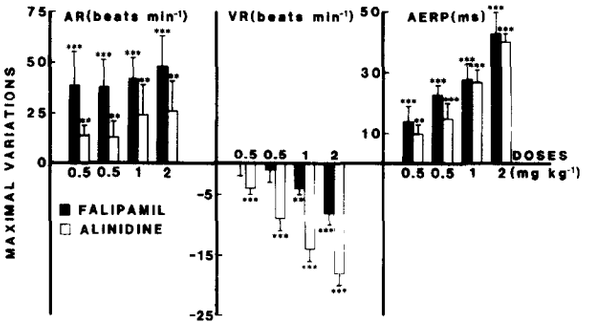

Fig. 2. Maximal effects on atrial rate (AR), ventricular rate (VR), and atrial effective refractory period (AERP) after four successive intravenous injections of 0.5, 0.5, 1, and 2 mg kg^{-1} falipamil hydrochloride (solid columns) and of the same doses of alinidine hydrobromide (open columns) in conscious AV-blocked dogs. Values are means for groups of six dogs. Vertical lines show S.E.M. ** $P < 0.01$, *** $P < 0.001$ in comparison with corresponding control values (80 ± 12 and 83 ± 9 beats min^{-1} for AR; 41 ± 2 and 41 ± 3 beats min^{-1} for VR; 125 ± 7 and 126 ± 6 ms for AERP, before falipamil and alinidine, respectively).

3.1.2. Corrected sinus recovery time

In the same dogs, falipamil shortened the corrected sinus recovery time at the highest dose ($P < 0.05$) (Fig. 1). This effect lasted 25 min and reached 51%. Conversely, alinidine lengthened the corrected sinus recovery time from the third dose onward ($P < 0.05$) (Fig. 1). This effect, which increased with dose, lasted 25 min and reached 71% at the highest dose.

3.1.3. Atrial rate

In AV-blocked dogs, falipamil increased the atrial rate from the first dose onward ($P < 0.001$) (Fig. 2), with a maximal effect of 61% at the highest dose. Alinidine also increased the atrial rate at all the doses used ($P < 0.01$) (Fig. 2), but with a maximal effect of only 31% at the highest dose. This effect appeared immediately after injection for both drugs and lasted ≥ 30 min and 15 min at the highest dose of falipamil and alinidine, respectively.

3.2. Effects on atrial myocardium refractoriness

Atrial refractoriness was assessed by measuring the atrial effective refractory period by the extrastimulus method in AV-blocked dogs. Falipamil increased the atrial effective refractory period at all the doses used ($P < 0.001$) (Fig. 2). This dose-related prolongation of the atrial effective refractory period reached 34% at the highest dose. Alinidine also prolonged the atrial effective refractory period at all the doses used ($P < 0.01$) (Fig. 2), with a maximal effect of 33% at the highest dose. This effect appeared immediately after injection and lasted ≥ 25 min at the highest dose of both drugs.

3.3. Effects on AV node refractoriness

AV nodal refractoriness was assessed by measuring Wenckebach point during right atrial pacing in intact dogs.

Falipamil increased Wenckebach point from the second dose onward ($P < 0.05$) (Fig. 1). This dose-related effect appeared immediately after injection, lasted ≥ 30 min and reached 62% at the highest dose. Conversely, alinidine decreased Wenckebach point at all the doses used ($P < 0.01$) (Fig. 1). This effect appeared immediately after injection, lasted ≥ 30 min and reached 35% at the highest dose.

3.4. Effects on His bundle automaticity

His bundle automaticity was assessed by measuring the ventricular rate in AV-blocked dogs. Falipamil decreased the ventricular rate from the third dose onward ($P < 0.01$) (Fig. 2). This ventricular bradycardic effect increased with dose, reaching 20% at the highest dose. Alinidine also decreased the ventricular rate at all the doses used ($P < 0.001$) (Fig. 2). This dose-related effect reached 44% at the highest dose. This effect appeared immediately after injection, and lasted ≥ 30 min at the highest dose of both drugs.

3.5. Effects on mean blood pressure

Neither falipamil nor alinidine significantly modified the mean blood pressure at any dose in either group (maximal variations of between -11 and $+9\%$).

4. Discussion

In conscious dogs, falipamil 0.5–4 mg kg^{-1} increased the sinus heart rate more markedly in AV-blocked (atrial rate) than in intact dogs (sinus rate). Such a tachycardic effect has already been reported in conscious dogs after falipamil at 5 mg kg^{-1}, when values of the control heart rate were low (Kobinger and Lillie, 1981). Conversely, falipamil decreased the ventricular rate, in complete agreement with a previous study under the same experimental conditions (Boucher et al., 1994). In addition, falipamil never caused mean blood pressure to vary as previously reported (Kobinger and Lillie, 1981). These results can be readily explained if the two following points are considered. First, falipamil has been reported to exhibit direct vagolytic properties (Kobinger and Lillie, 1981; Osterrieder et al., 1981); second, in conscious intact or AV-blocked dogs, the atria are under strong vagal tone (Robinson et al., 1973; Boucher et al., 1979; Chassaing et al., 1979; Rigel et al., 1984), and in conscious AV-blocked dogs, the ventricles are under very weak vagal tone (Boucher et al., 1979; Li et al., 1986). Thus the decrease in ventricular rate results from the true bradycardic effect of falipamil (Dämmgen et al., 1981; Kobinger and Lillie, 1981; Lillie and Kobinger, 1983) without (or almost without) any interference from its vagolytic properties, whereas the increases in sinus rate and atrial rate are most likely due to the direct vagolytic action of falipamil. This tachycardic effect is buffered by the direct bradycardic effect of falipamil and, in addition for the atrial rate, potentiated by a ventricular bradycardia-induced reflex tachycardic effect. Comparatively, alinidine 0.5–4 mg kg^{-1} increased the atrial rate less markedly and decreased the ventricular rate more markedly than falipamil, and decreased the sinus rate, indicating that falipamil exerts less marked bradycardic effects, most likely associated with more marked vagolytic effects than alinidine. A previous study (Boucher et al., 1989) has already pointed out the role of its vagolytic effect in the increase in atrial rate produced by alinidine.

Simultaneously, falipamil shortened the corrected sinus recovery time in intact dogs, but only at the highest cumulative dose of 4 mg kg^{-1}. The difference for the sinus rate (increase at the two highest doses) can be ascribed to the variability of the corrected sinus recovery time parameter. This shortening of the corrected sinus recovery time is readily explained by the vagolytic action of falipamil. Falipamil increased Wenckebach point, reflecting an increase in AV conduction speed. This positive dromotropic effect also very likely results from the vagolytic action of falipamil. Our result conflicts with the findings of (i) Kawada et al. (1984), who showed an increase in AV nodal conduction time after falipamil 1 mg in the isolated canine AV node, (ii) Takeda et al. (1989), who reported an increase in AV conduction time after falipamil 3 mg injected into the AV node artery of anaesthetized dogs, and (iii) Kobinger and Lillie (1981), who reported practically no change in P-Q interval after falipamil ≤ 10 mg kg^{-1} i.v. in anaesthetized cats. However, these discrepancies can be readily explained because except for our study, which was performed in conscious dogs in which vagal tone is fully expressed, all the conflicting data were obtained either in vitro or in vivo in animals under anaesthesia. The well-known vagolytic effect of anaesthesia (Greisheimer, 1965; Olmsted and Page, 1966; Lindmar et al., 1979) prevents falipamil from fully expressing its vagolytic properties. Comparatively, alinidine prolonged the corrected sinus recovery time, but only at the two highest doses, and decreased Wenckebach point, reflecting a decrease in AV conduction. These results confirm the predominance of the vagolytic effect of falipamil (when it can be expressed) over its true cardioinhibitory effects, and the reverse for alinidine.

Falipamil also prolonged the atrial effective refractory period. This effect reached 34% at the cumulative dose of 4 mg kg^{-1}, in agreement with the result of the only study reported in the literature concerning this parameter (Kobinger and Lillie, 1981), which showed a decrease of 30% in the maximal atrial driving frequency at 19 μg ml^{-1} falipamil in isolated guinea pig atria. This effect is also consistent with the results of all the studies showing an increase in action potential duration after falipamil addition (Osterrieder et al., 1981; Trautwein et al., 1981; Hohnloser et al., 1982; Pelzer et al., 1982). This prolonga-

tion of the atrial effective refractory period, which suggests that falipamil has antiarrhythmic potential, does not seem to result from its vagolytic effect (or only in very small part), since inhibition of vagal tone obtained in other circumstances gave a lengthening of the atrial effective refractory period of less than 10 ms (Boucher et al., 1986). Alinidine produced the same effect as falipamil, i.e., an increase of the atrial effective refractory period reaching 34% at the highest dose of 4 mg kg^{-1}. This effect on the atrial effective refractory period is important, since under the same experimental conditions quinidine, the well-known class IA antiarrhythmic agent, lengthened the atrial effective refractory period by 28% at a cumulative dose of 4 mg kg^{-1} (Boucher et al., 1991).

Overall, our results show that falipamil exhibits electrophysiological effects, i.e., increase in sinus rate and atrial rate, shortening of the corrected sinus recovery time, and increase in Wenckebach point, which reflect the predominant direct vagolytic effect of this drug, whereas alinidine produces effects, i.e., decrease in sinus rate and ventricular rate, lengthening of the corrected sinus recovery time and of the atrial effective refractory period, and decrease in Wenckebach point, corresponding to the marked antiarrhythmic potential of this agent. This is an instance of two drugs with almost identical specific bradycardic properties producing quite different electrophysiological effects in the conscious dog.

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