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Cardiac electrophysiological effects of propafenone and its 5-hydroxylated metabolite in the conscious dog

Michel Boucher [a,b,*], Claude Chassaing [a], Jean-Dominique Hamel [c], Jean-Marie Poirier [d]

[a] *INSERM U195, Faculty of Medicine, Clermont-Ferrand, France*
[b] *Department of Physiology, Faculty of Pharmacy, Clermont-Ferrand, France*
[c] *Knoll France Laboratories, Levallois-Perret, France*
[d] *Department of Pharmacology, St.-Antoine Hospital, Paris, France*

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Abstract

We studied the cardiac electrophysiological effects of propafenone and its 5-hydroxylated metabolite in conscious dogs. Sinus rate, corrected sinus recovery time and Wenckebach point were measured in 6 intact dogs. Atrial rate, ventricular rate and atrial effective refractory period were measured in 6 atrioventricular-blocked dogs. In both groups, we also determined blood pressure and plasma drug concentrations. Each dog received, with at least an 8-day interval, propafenone (hydrochloride) and 5-hydroxypropafenone (hydrochloride) in 4 successive intravenous injections, 30 min apart, at 0.5, 0.5, 1 and 2 mg kg^{-1}. Propafenone increased sinus rate and atrial rate more markedly than 5-hydroxypropafenone, and also transiently ventricular rate, whereas 5-hydroxypropafenone decreased it weakly. Propafenone shortened corrected sinus recovery time and increased Wenckebach point at the highest dose only, whereas 5-hydroxypropafenone did not modify corrected sinus recovery time and increased Wenckebach point less markedly than propafenone. Both drugs produced an identical atrial effective refractory period lengthening. Propafenone either increased mean blood pressure (in intact dogs) or decreased it (in atrioventricular-blocked dogs) at the highest dose only, whereas 5-hydroxypropafenone did not produce any effect on this parameter. Overall, these results show that propafenone and 5-hydroxypropafenone exhibit cardiac electrophysiological effects, reflecting (a) direct vagolytic action for both drugs associated with cardiodepressant effects for 5-hydroxypropafenone, and (b) marked atrial antiarrhythmic properties for 5-hydroxypropafenone probably involved in the therapeutic effect of propafenone.

Keywords: Propafenone; 5-Hydroxypropafenone; Sinoatrial node automaticity; His bundle automaticity; Atrial myocardium refractoriness; AV node refractoriness; Blood pressure; (Conscious intact dog); (AV-blocked dog)

1. Introduction

Propafenone is an antiarrhythmic drug which belongs to class Ic of the classification of Vaughan Williams, producing a use-dependent effect on phase 0 of the action potential with differential changes on the action potential duration according to the tissue considered (Kohlhardt and Seifert, 1980; Ledda et al., 1981; Dukes and Vaughan Williams, 1984; Katoh et al., 1987; Rouet et al., 1989). It also exhibits relatively weak beta-blocking and calcium entry-blocking properties (Ledda et al., 1981; Dukes and Vaughan Williams, 1984; Delgado et al., 1985). This drug has been found to be effective against various clinical arrhythmias (Beck et al., 1978; Marshall and Winslow, 1982; Connolly et al., 1983; De Soyza et al., 1984; Naccarella et al., 1984; Bertini et al., 1990; Budde et al., 1991). Propafenone is extensively metabolized, undergoing mainly oxidative metabolism to produce 5-hydroxypropafenone, the plasma concentrations of which may reach high values during chronic therapy (Kates et al., 1985). Given the in vitro electrophysiological properties, i.e., reduction of the maximum upstroke velocity of phase 0 of the action potential and lengthening of effective refractory period (Delgado et al., 1987; Malfatto et al., 1988; Thompson et al., 1988; Rouet et al., 1989; Case et al., 1991), and the antiarrhythmic actions (Von Philipsborn et al., 1984; Harron and Brogden, 1987; Malfatto et al., 1988) exhibited by 5-hydroxypropafenone, it has been suggested that it may contribute to the therapeutic or toxic effects of the parent compound.

* Corresponding author. Department of Physiology, Faculty of Pharmacy, F-63001 Clermont-Ferrand Cedex 1, France. Fax: (33) 7327-7907.

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To our knowledge, no comparative electrophysiological study of propafenone and 5-hydroxypropafenone had been performed hitherto in conscious animals. We therefore studied the effects of both drugs on sinoatrial node and His bundle automaticities, atrial myocardium and atrioventricular (AV) node refractoriness, and blood pressure as a function of dose in conscious dogs. The use of conscious dogs and plasma drug concentrations roughly covering the assumed therapeutic range was designed to give the results greater predictive value.

2. Materials and methods

Twelve mongrel dogs of either sex weighing 15–24 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 6 dogs (intact dogs) out of the 12, 2 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 6 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 6 dogs) and an arterial catheter (in 3 dogs) were implanted as described. All dogs were left to recover for at least 8–10 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 8 pacing stimuli. During recording, the previously trained dogs were placed on a table and lightly restrained. Two microcatheters were fitted before each test, one in the cephalic vein and the other in a branch of the saphenous vein, to allow painless drug administration and blood sampling, respectively.

2.3. Protocol

Propafenone (hydrochloride) and 5-hydroxypropafenone (hydrochloride) 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 4 successive intravenous (i.v.) injections, lasting 30 s each, of each drug, 30 min apart. The experiments were carried out at least 8–10 days postoperatively, by wich time the dogs were thoroughly familiarized with the experimental conditions. At least an 8-day interval elapsed between each drug evaluation performed on the same dog 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). To measure plasma propafenone and 5-hydroxypropafenone concentrations, blood samples were collected in 3 of the dogs in each experimental series 5, 20, and 30 min after each injection. The plasma was immediately separated by centrifuging, and frozen until assay. Plasma propafenone concentrations were determined using the specific high-performance liquid chromatography method described by Harapat and Kates (1982) and plasma 5-hydroxypropafenone concentrations using the specific high-performance liquid chromatography method of Hoyer (1988).

2.4. Drugs

Propafenone (hydrochloride) and 5-hydroxypropafenone (hydrochloride) were supplied by Biosedra Laboratories (Malakoff, France). 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 at the time by which maximal or minimal value had been 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. The correlation lines relating the different parameters to the log plasma drug concentrations were computed, whenever possible, and the significance of the correlation coefficients was determined. Plasma drug concentrations in the 2 experimental series were compared using areas under the curves obtained by plotting the concentrations against time.

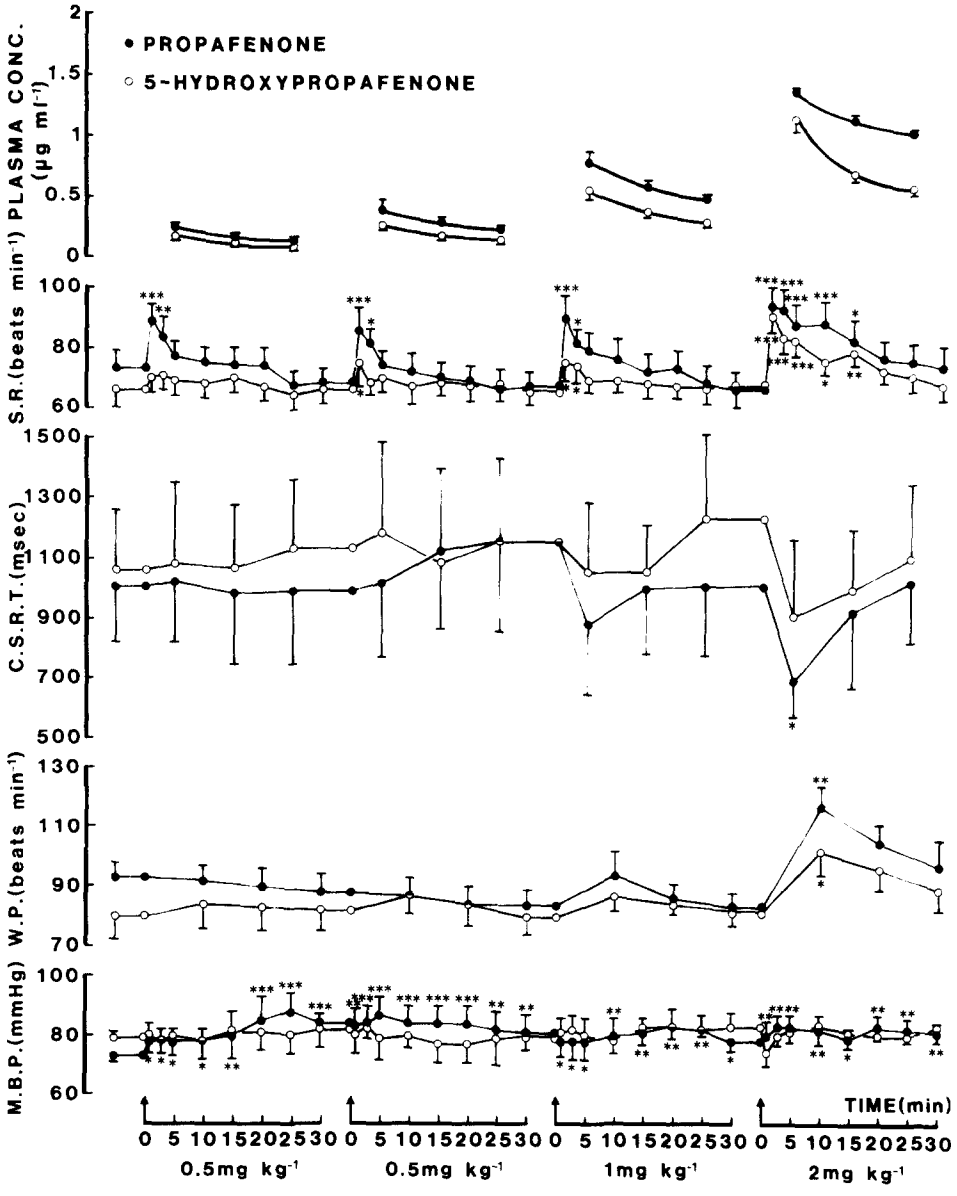

Fig. 1. Changes in plasma concentration, sinus rate (SR), corrected sinus recovery time (CSRT), Wenckebach point (WP) and mean blood pressure (MBP) in conscious intact dogs after 4 successive i.v. injections (arrows) of 0.5, 0.5, 1 and 2 mg kg^{-1} of propafenone hydrochloride (●) and of 5-hydroxypropafenone hydrochloride (○). Values are means for groups of 6 dogs, except for plasma concentration and mean blood pressure (only 3 dogs). Vertical lines show S.E.M. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$ in comparison with corresponding control values.

3. Results

3.1. Plasma concentrations of propafenone and 5-hydroxypropafenone

The time courses of mean plasma propafenone and 5-hydroxypropafenone concentrations in the 2 experimental series are shown in Figs. 1 and 2. According to the dose administered, the maximal plasma concentrations of propafenone lay between 0.24 ± 0.04 and 1.35 ± 0.04 μg ml^{-1} in intact dogs and between 0.52 ± 0.02 and 1.97 ± 0.23 μg ml^{-1} in AV-blocked dogs, and the minimal concentrations, 25 min after injection, were between 0.12 ± 0.02 and 1.00 ± 0.04 μg ml^{-1} in intact dogs and 0.16 ± 0.02 and 1.02 ± 0.06 in AV-blocked dogs, i.e., roughly covering the assumed therapeutic range (0.5–2.0

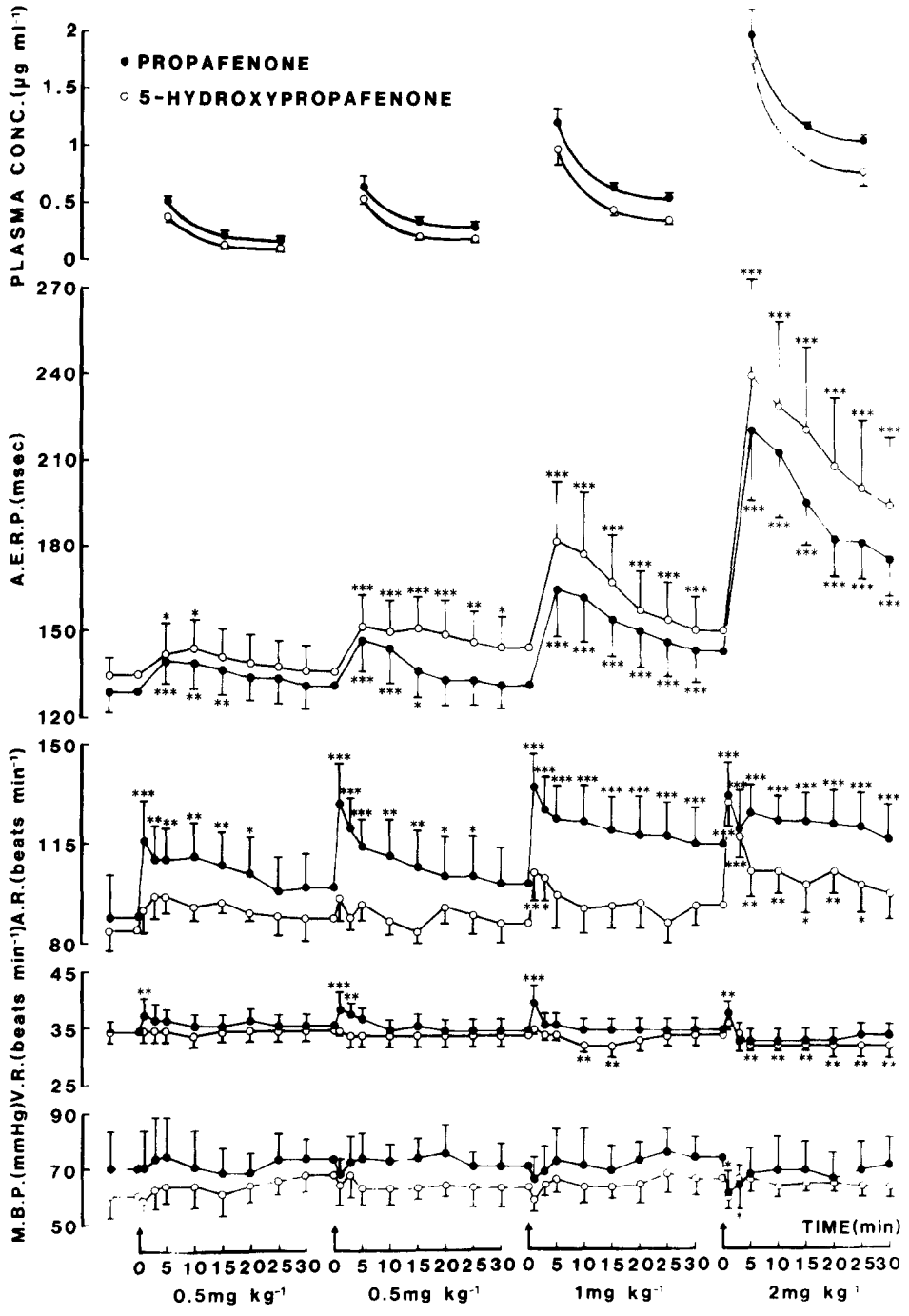

Fig. 2. Changes in plasma concentration, atrial effective refractory period (AERP), atrial rate (AR), ventricular rate (VR) and mean blood pressure (MBP) in conscious atrioventricular-blocked dogs after 4 successive i.v. injections (arrows) of 0.5, 0.5, 1 and 2 mg kg^{-1} of propafenone hydrochloride (●) and of 5-hydroxypropafenone hydrochloride (○). Values are means for groups of 6 dogs, except for plasma concentration and mean blood pressure (only 3 dogs). Vertical lines show S.E.M. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$ in comparison with corresponding control values.

$\mu g\ ml^{-1}$) (Seipel and Breithardt, 1980). The plasma concentrations of 5-hydroxypropafenone ranged from 0.09 ± 0.01 to $1.13 \pm 0.10\ \mu g\ ml^{-1}$ in intact dogs and from 0.10 ± 0.01 to $1.76 \pm 0.29\ \mu g\ ml^{-1}$ in AV-blocked dogs. As confirmed by the areas under the curves, the plasma concentrations of propafenone were higher than those of 5-hydroxypropafenone in either series ($P < 0.05$), and the plasma concentrations of both drugs were higher in the AV-blocked dog series ($P < 0.05$).

3.2. Effects on sinoatrial node automaticity

3.2.1. Sinus rate

In intact dogs, propafenone increased sinus rate from the first dose onward ($P < 0.001$) (Fig. 1). This tachycardic effect, which appeared immediately after injection, increased with dose, reaching 22, 26, 34 and 42%, and lasting 3, 3, 3 and 15 min, respectively. 5-Hydroxypropafenone increased sinus rate only from the second dose onward ($P < 0.05$) (Fig. 1). This effect, which appeared immediately after injection, was similar at the 2nd and 3rd doses (14%, and 1 and 3 min) and markedly increased at the highest dose of 4 mg kg^{-1} (34% and 15 min).

3.2.2. Corrected sinus recovery time

In these intact dogs, propafenone shortened corrected sinus recovery time only at the 5th min after the injection of the highest dose ($P < 0.05$) (Fig. 1). This effect reached 31%. 5-Hydroxypropafenone had no effect on this parameter.

3.2.3. Atrial rate

The difference observed between the effects of propafenone and 5-hydroxypropafenone on sinus rate in intact dogs was even more marked on atrial rate in AV-blocked dogs. In these dogs, propafenone increased atrial rate from the first dose onward ($P < 0.001$) (Fig. 2). This tachycardic effect, which appeared immediately after injection, increased with dose, reaching 30, 45, 51 and 48%, and lasting 20, 25, ≥ 30 and ≥ 30 min, respectively, with a significant correlation ($r = 0.60$, $P < 0.001$) between atrial rate increases and plasma propafenone concentrations. 5-Hydroxypropafenone increased atrial rate only at the 2 highest doses ($P < 0.01$) (Fig. 2), this effect reaching 56% and lasting 25 min at the dose of 4 mg kg^{-1}.

3.3. Effects on atrial myocardium refractoriness

Atrial refractoriness was assessed by measuring atrial effective refractory period by the extrastimulus method in AV-blocked dogs. Propafenone increased atrial effective refractory period at all the doses used ($P < 0.001$) (Fig. 2). This dose-related effect, which appeared immediately after injection, reached 9, 14, 28 and 72%, and lasted 15, 15, ≥ 30 and ≥ 30 min, respectively, with a significant correlation ($r = 0.80$, $P < 0.001$) between atrial effective refractory period increases and plasma propafenone concentrations. 5-Hydroxypropafenone produced a similar atrial effective refractory period prolonging effect (Fig. 2), reaching between 5 and 78% and lasting between 10 and ≥ 30 min, with a significant correlation ($r = 0.76$, $P < 0.001$) between atrial effective refractory period increases and plasma concentrations.

3.4. Effects on AV node refractoriness

AV nodal refractoriness was assessed by measuring Wenckebach point during right atrial pacing in intact dogs. Both drugs only increased Wenckebach point at the 10th min of the highest dose (Fig. 1). This effect reached 41% ($P < 0.01$) for propafenone and 28% ($P < 0.05$) for 5-hydroxypropafenone.

3.5. Effects on His bundle automaticity

His bundle automaticity was assessed by measuring ventricular rate in AV-blocked dogs. Propafenone briefly (between 1 and 3 min) increased ventricular rate from the first dose onward ($P < 0.01$) (Fig. 2). This tachycardic effect reached 9, 12, 15 and 10%, respectively. Conversely, 5-hydroxypropafenone decreased ventricular rate at the 2 highest doses ($P < 0.01$) (Fig. 2). This bradycardic effect reached 9% for the 2 doses.

3.6. Effects on mean blood pressure

Propafenone increased mean blood pressure at all doses in intact dogs ($P < 0.05$) (Fig. 1) and decreased it at the highest dose in AV-blocked dogs ($P < 0.05$) (Fig. 2). These effects reached between 14 and 20% in intact dogs and 14% in AV-blocked dogs. Conversely, 5-hydroxypropafenone did not modify this parameter at any dose in either series.

4. Discussion

In conscious dogs, propafenone 0.5–4 mg kg^{-1} increased sinus heart rate more markedly in AV-blocked (atrial rate) than in intact dogs (sinus rate). A tachycardic effect has already been reported after propafenone in humans (McLeod et al., 1984) and in conscious AV-blocked dogs (Li et al., 1986a). In addition, propafenone produced an initial (≤ 3 min) increase in ventricular rate. Given that (1) in conscious intact or AV-blocked dogs atria are under strong vagal tone (Robinson et al., 1973; Boucher et al., 1979; Chassaing et al., 1979; Rigel et al., 1984), (2) in conscious AV-blocked dogs ventricles are under weak vagal tone (Li et al., 1986b; Boucher et al., 1994a,b) and (3) propafenone either increased mean blood pressure in intact dogs or did not modify it (at least at the first 3 doses) in AV-blocked dogs, the tachycardic effects are

most likely due to a direct vagolytic action of propafenone. Such a vagolytic activity has already been demonstrated in conscious AV-blocked dogs given atropine before propafenone (Li et al., 1986a). Comparatively, 5-hydroxypropafenone 0.5–4 mg kg^{-1} increased sinus rate and atrial rate less markedly, and decreased ventricular rate, admittedly weakly, suggesting that 5-hydroxypropafenone exhibits more marked cardiodepressant effects than propafenone, which counteract its vagolytic action.

Simultaneously, at the highest dose, propafenone shortened corrected sinus recovery time, whereas 5-hydroxypropafenone did not modify it, and increased Wenckebach point, which reflects an increase in AV conduction velocity, more markedly than 5-hydroxypropafenone. These effects observed at plasma concentrations ≥ 0.930 and 0.461 $\mu g\ ml^{-1}$, respectively, are consistent with the above interpretation, i.e., direct vagolytic action for both drugs associated with a more or less complete buffering by cardiodepressant effects for 5-hydroxypropafenone. These results conflict with the findings of (1) Delgado et al. (1987), who showed a dose-dependent increase in sinus node recovery time after 5-hydroxypropafenone in isolated guinea-pig atria, (2) Von Philipsborn et al. (1984), who reported a prolongation of A-H interval after both propafenone and 5-hydroxypropafenone in sodium pentobarbital anaesthetized dogs, and (3) Haefeli et al. (1991), who reported an increase in P-Q interval after 5-hydroxypropafenone concentrations $\leq 0.337\ \mu g\ ml^{-1}$ in normal subjects. However, these discrepancies can be readily explained; all the conflicting data were obtained either in vitro or in vivo in animals under sodium pentobarbital anaesthesia, i.e., under experimental conditions under which vagolytic action of tested drugs cannot be fully expressed, and in humans at concentrations lower than in our study.

Propafenone and 5-hydroxypropafenone also prolonged atrial effective refractory period. This effect, which was related to dose and plasma concentration, reached 71 and 76% at the cumulative dose of 4 mg kg^{-1}, i.e., at plasma levels of 1.97 and 1.76 $\mu g\ ml^{-1}$ for propafenone and 5-hydroxypropafenone, respectively. This result agrees with those of studies performed on isolated guinea-pig atrial fibres (Delgado et al., 1985, 1987), on isolated guinea-pig and rabbit atria (Von Philipsborn et al., 1984; Kerr, 1990), and on atrial tissue in anaesthetized dogs (Villafane et al., 1987), and is also consistent with the results of all the studies showing an increase in atrial action potential duration (Dukes and Vaughan Williams, 1984; Delgado et al., 1987; Katoh et al., 1987). This atrial effective refractory period effect is very important, since under the same experimental conditions quinidine, the well-known Ia antiarrhythmic agent, produced an atrial effective refractory period lengthening of 28% at a cumulative dose of 4 mg kg^{-1} (Boucher et al., 1991). The vagolytic action of either drug is not involved (or only to a very small degree), since inhibition of vagal tone obtained in other circumstances gave a lengthening of atrial effective refractory period of < 10 ms (Boucher et al., 1986) compared to about 100 ms here, and this effect mainly results from the membrane stabilizing properties of both drugs on ionic currents. In addition, the activity ratio of about 1 observed with plasma levels covering the therapeutic range strongly suggests that 5-hydroxypropafenone is significantly involved in the antiarrhythmic properties of propafenone.

Overall, our results show that 5-hydroxypropafenone exhibits electrophysiological effects, i.e., increases in sinus rate, atrial rate and Wenckebach point lower than those produced by propafenone, decrease in ventricular rate, no effect on corrected sinus recovery time, and marked increase in atrial effective refractory period identical to that produced by propafenone, reflecting direct vagolytic action for both drugs associated with cardiodepressant effects for 5-hydroxypropafenone, and marked atrial antiarrhythmic properties for 5-hydroxypropafenone probably involved in the therapeutic effect of propafenone.

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