Comparison Between *Propafenone* and *Digoxin* Administered Intravenously to Patients With Acute Atrial Fibrillation

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In recent-onset atrial fibrillation, intravenous propafenone has been shown to effectively restore sinus rhythm, whereas the efficacy of intravenous digoxin has been questioned. We directly compared these 2 drugs and placebo in acute atrial fibrillation. One hundred twenty-three patients with atrial fibrillation lasting <72 hours were randomized to a 10-minute intravenous infusion of either propafenone (2 mg/kg, 41 patients) or digoxin (0.007 mg/kg, 40 patients) or placebo (42 patients). After 1 hour, nonconverted propafenone or digoxin patients were switched to the alternative drug, while nonconverted placebo patients were randomized to either propafenone or digoxin. The observation time ended 1 hour later. By 1 hour, conversion rates were 49% in the propafenone group, 32% in the digoxin group (p = 0.12), and 14% in placebo group (p <0.001 vs propafenone, p = 0.08 vs digoxin). After crossover, digoxin converted 5% of propafenone patients, while propafenone converted 48% of digoxin patients (p <0.05). In the 36 nonconverted placebo patients, sinus rhythm was obtained in 53% of cases with propafenone, and in 5% with digoxin (p <0.05). Globally, among the 116 patients who received a drug as first treatment, 30 of 60 patients (50%) were converted by propafenone versus 14 of 56 (25%) by digoxin (p <0.01) (odds ratio 2.0, 95% confidence interval 1.19 to 3.36). In nonconverters, the ventricular rate reduction was faster (15 vs 45 minutes) and more prominent (−24% vs −14%) with propafenone than with digoxin. In conclusion, intravenous propafenone terminates atrial fibrillation more effectively than either placebo or intravenous digoxin. In addition, in nonconverted patients, it obtains a more rapid and marked control of the ventricular rate.

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Atrial fibrillation of recent onset is the arrhythmia that most often prompts patients to seek help in the hospital emergency room.[1] The optimal therapy for patients in this setting remains controversial. Intravenous digitalis is considered to have a prominent role in the acute management of atrial fibrillation[2,3] and, despite its questionable efficacy,[4] it is still the drug most widely administered for acute management of this arrhythmia.[5] In the last decade, antiarrhythmic class IC agents have been effective in the rapid termination of recent-onset atrial fibrillation,[6–8] and are now increasingly used for this indication. However, no placebo-controlled study directly comparing a class IC drug with digitalis has been conducted. The aim of the present study was thus to compare intravenous propafenone with intravenous digoxin (both matched with placebo) in patients entering the emergency room because of acute atrial fibrillation.

METHOD

This single-blind, placebo-controlled study included all patients aged between 18 and 75 years presenting at the emergency room of any of the 10 Italian participating hospitals (see Appendix), with atrial fibrillation lasting from 1 to 72 hours. Exclusion criteria were any of the following: ongoing digitalis or class I or III antiarrhythmic drug therapy, myocardial infarction within the preceding month, postoperative period after heart surgery, unstable angina, clinical signs of heart failure or low cardiac output, clinical signs of hyperthyroidism, systolic blood pressure <100 mm Hg, heart rate <80 beats/min, bifascicular block, known sick sinus syndrome or second- or third-degree atrioventricular block in absence of a cardiac pacemaker, Wolff-Parkinson-White syndrome, and ascertained or presumed pregnancy.

Study design: The study was designed in order to reproduce the real situation of an emergency room, where time is limited and protracted infusions with concomitant patient's monitoring are impractical. Therefore, we planned only a short intravenous bolus of the drugs, not followed by continuous infusion, limiting the observation time to 1 hour.

After having undergone baseline electrocardiography, a blood sample for routine laboratory examination, and a medical history and physical examination, eligible patients were randomly assigned to receive a 10-minute intravenous infusion of either propafenone 2 mg/kg, digoxin 0.007 mg/kg, or placebo (50 ml in saline solution). Patients underwent continuous oscilloscopic monitoring from the beginning of the infusion until completion of the study. A 12-lead electrocardiogram and blood pressure measurement were obtained at baseline, and 15, 30, 45, and 60 minutes after the start of infusion. If sinus rhythm was not restored within 1 hour, patients who had received an active drug were switched to the alternative one, whereas those who had received placebo were randomized to either propafenone or digoxin. The drugs were then

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TABLE I Baseline Characteristics of Patients

	Propafenone (n = 41)	Digoxin (n = 40)	Placebo (n = 42)
Age (yr)	59 ± 13	59 ± 12	61 ± 14
Weight (kg)	75 ± 12	76 ± 11	74 ± 14
Men	26 (63%)	19 (48%)	19 (45%)
Arrhythmia duration (hr)	14 ± 17	13 ± 18	14 ± 20
Organic heart disease	28 (68%)	23 (58%)	22 (52%)
Hypertension	11 (27%)	13 (32%)	12 (29%)
Previous AF	20 (48%)	29 (72%)	23 (55%)
Concomitant CV therapy	17 (32%)	21 (53%)	18 (43%)
Mean ventricular rate (beats/min)	144 ± 24	144 ± 22	136 ± 25

Data are presented as number (%) of patients or mean value ± SD.
There was no significant difference between the 3 groups.
AF = atrial fibrillation; CV = cardiovascular.

infused with the same method of administration and patients were followed up, as described for the first treatment, for a further hour.

The end points of the study were: (1) conversion to sinus rhythm within 1 hour from the start of the first treatment, (2) conversion to sinus rhythm within 1 hour from the start of the second treatment, (3) ventricular rate in nonconverters, and (4) frequency and severity of side effects.

The study was approved by the local ethical committees of the participating centers and informed consent was obtained from each patient.

Sample size: The conversion rates within the first hour were estimated to be about 50% for propafenone[8,9] and 15% for placebo.[6,10] On the basis of the available data,[4] digoxin was expected to have a conversion rate similar to placebo. Given an α error of 0.05 and a 1-β error of 90%, it was calculated that 40 patients per arm would be sufficient to detect such a significant difference.

Randomization procedure: Randomization was performed by each center using a computer-generated "ad hoc" list (1 for each center) guaranteeing that groups were balanced every 6 patients.

Statistical analysis: Data were analyzed according to primary, secondary, and combined success rate. The 2-sided Fisher exact test or chi-square test was used for frequency analysis. Differences in continuous variables were analyzed by 1-way analysis of variance and groups were compared with use of the multiple Bonferroni test. The relative efficacy of the study treatments was assessed by relative risk analysis[11] and differences in the time to conversion were analyzed by the method of Kruskal-Wallis. Differences in atrial fibrillation duration between converters and nonconverters were analyzed by the Mann-Whitney U test. All statistics were expressed as a mean ± SD. A p value <0.05 was considered significant.

RESULTS

Study patients: One hundred twenty-five patients were enrolled in the trial. Two were excluded from the study because conversion to sinus rhythm occurred before randomization and 123 were allocated to treatment: 41 to propafenone, 40 to digitalis, and 42 to placebo. The study groups did not differ in terms of baseline characteristics (Table I).

Conversion to sinus rhythm after the first treatment: Figure 1 shows the management tree of our study patients. Within the 1-hour period after administration of the first treatment, reversion to sinus rhythm was observed in 20 patients (49%) taking propafenone, in 13 patients (32%) taking digitalis, and in 6 patients (14%) assigned to placebo. Results with propafenone were significantly superior to those with placebo (odds ratio [OR] 3.41, 95% confidence interval [CI] 1.53 to 7.63, $p<0.001$). There was a nonsignificant trend toward a better performance with propafenone than with digoxin (OR 1.5, 95% CI 0.87 to 2.59, $p = 0.12$) and with digoxin versus placebo (OR 2.29, 95% CI 0.96 to 5.40, $p = 0.08$). The time from the start of infusion to conversion was 31 ± 20 minutes for propafenone, 34 ± 17 minutes for digitalis, and 38 ± 21 for placebo (p = NS).

Predictors of conversion: The following variables were considered for a possible association with reversion to sinus rhythm: sex, age, concomitant therapy, underlying heart disease, previous atrial fibrillation, baseline ventricular rate, and duration of the arrhythmia. Not 1 variable was found to be associated with arrhythmia reversion except for the duration of atrial fibrillation, which was significantly shorter in patients who converted to sinus rhythm (328 ± 326 minutes) than in those who did not (494 ± 511 minutes) ($p = 0.03$).

Reversion to sinus rhythm after the second treatment: Two noncardioverted patients, 1 from the propafenone group and 1 from the placebo group, were not randomized to the second treatment because their ventricular rate was <80 beats/min.

By the end of the second observation time, only 1 of the 20 patients (5%) assigned to digoxin after failure with propafenone was converted to sinus rhythm, whereas 13 of the 27 patients (48%) resistant to digitalis reverted to sinus rhythm with propafenone ($p<0.05$). In the 36 nonconverted placebo patients, sinus rhythm was obtained in 10 of 19 (53%) assigned to propafenone and in 1 of 16 (5%) assigned to digoxin ($p<0.05$). In the latter group, conversion time was 29 ± 19 minutes with propafenone and 35 minutes for the only patient converted by digoxin (p = NS).

By considering patients initially randomized to propafenone or digoxin and those randomized to the same drugs after placebo failure, 116 received an active drug as first treatment: 60 propafenone and 56 digoxin. Conversion rates were 50% (30 patients) with propafenone and 25% (14 patients) with digoxin (OR 2.0, 95% CI 1.19 to 3.36, $p<0.01$).

Heart rate in nonconverters: Heart rate at baseline, and at 15, 30, 45, and 60 minutes in patients who

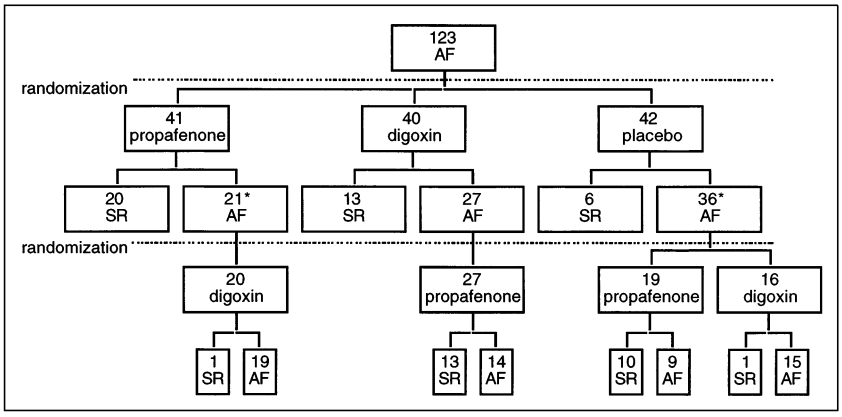

FIGURE 1. Randomization tree of study patients. Numbers indicate the number of patients. AF = atrial fibrillation; SR = sinus rhythm; *1 patient excluded because of heart rate <80 beats/min.

remained in atrial fibrillation after the first treatment are reported in Table II. Figure 2 shows the time course of heart rate with respect to baseline in the 3 groups of patients. Within each group there was a significant reduction in heart rate with respect to baseline at all times ($p < 0.01$), except for placebo at 15 minutes. At 15 and 30 minutes, heart rate reduction was similar in digoxin- and placebo-treated patients (−9% and −10% vs −4% and −7%, respectively, p = NS), whereas it was more prominent in patients treated with propafenone (−24%, $p < 0.001$ vs both digoxin and placebo). At 45 minutes, the heart rate decrease induced with digoxin, although still significantly inferior to that induced with propafenone, became greater than that observed with placebo (−12% vs −6%, $p < 0.05$). At 60 minutes, digoxin- and propafenone-treated patients had similar heart rates (−14% vs −16%, p = NS), both significantly lower than those in placebo patients (−5%, $p < 0.05$).

Adverse effects: No serious adverse events were observed in any patients. Four of the 87 patients (5%) (p = 0.12 vs digitalis) who received propafenone had hypotension (systolic blood pressure between 70 and 90 mm Hg) between 8 and 45 minutes from the start of drug infusion. In 2 patients the phenomenon was associated with sinus bradycardia (40 and 55 beats/min, respectively), nausea, and slight malaise. In all the cases hypotension rapidly resolved with saline infusion and discontinuance of drug administration (1 patient).

Atrial fibrillation was transformed in asymptomatic atrial flutter with 2:1 atrioventricular conduction (ventricular rates between 105 and 130 beats/min) in 3 patients: 1 taking propafenone as first treatment, 1 taking propafenone after digoxin, and 1 taking digoxin after propafenone.

DISCUSSION

The use of digitalis in acute atrial fibrillation was first reported in 1835[12] and, since then, it has represented the standard treatment in this setting.[2] Although data from uncontrolled studies[13,14] supported the belief that digoxin could restore sinus rhythm, 3 controlled trials[4,15,16] demonstrated no difference in conversion rates between digoxin and placebo. Conversely, the initial observational studies on propafenone, reporting success rates between 45% and 66% in acute atrial fibrillation,[7–9,17] have been confirmed by subsequent controlled trials.[18–20]

To our knowledge, the present placebo-controlled study is the first to directly compare propafenone with digoxin—both administered as a short intravenous infusion—in patients with recent-onset atrial fibrillation. The observation period was short (1 hour) in order to simulate the limited time available in the emergency room.

Conversion to sinus rhythm: In the present study, half of the patients with recent-onset atrial fibrillation had conversion to sinus rhythm within 1 hour by a single intravenous bolus of propafenone. Suttorp et al,[8] using the same administration protocol and observation time, obtained a similar conversion rate (55%). In 2 studies, both using a 2–mg/kg bolus dose followed by continuous drug infusion for 3 hours, intravenous propafenone was found to be more effective in restoring sinus rhythm than either placebo (59% vs 31%, $p < 0.01$) or digitalis (88% vs 32%, $p < 0.001$). The long observation times and the continuous drug infusion after the bolus dose can account for these high conversion rates.

In our hands, conversion to sinus rhythm by 1 hour with digoxin was higher than expected (32%), leading to a trend (p = 0.08) toward a better performance of the drug versus placebo (conversion rate 14%). The very low efficacy of the drug (5%) when given as second treatment could indicate this trend was simply due to chance.

Indeed, the difference between the efficacy of propafenone and digoxin—although not apparent at the end of the first hour—becomes significant when the results of the first treatment are combined with those obtained after the second treatment in the nonconverted placebo patients (50% vs 25%). Moreover, after drug crossover, propafenone was significantly more effective than digoxin (48% vs 5%). It can be thus concluded that intravenous digoxin is less effective than intravenous propafenone in converting atrial fibrillation to sinus rhythm.

It has been observed that after 24 hours of observation, the percent reversion to sinus rhythm is high and substantially similar, regardless of whether patients had received an antiarrhythmic agent or placebo.[21,22] Digitalis could thus be justified as a therapeutic option intended to reduce heart rate, while waiting for a spontaneous termination of the arrhythmia.[2,16] However, letting nature "run its course" may have its

TABLE II Time Course of Heart Rate in Patients Who Did Not Convert to Sinus Rhythm by the First Hour

	Baseline (beats/min)	15 Minutes (beats/min)	30 Minutes (beats/min)	45 Minutes (beats/min)	60 Minutes (beats/min)
Propafenone (n = 21)	138 ± 22	109 ± 22*†	105 ± 25*†	112 ± 22*	115 ± 21*‡
Digoxin (n = 27)	143 ± 23	130 ± 26*	128 ± 25*	126 ± 25*‡	123 ± 27*‡
Placebo (n = 36)	135 ± 26	120 ± 23	126 ± 24*	127 ± 25*	128 ± 24*

*p <0.01 versus baseline; †p <0.001 versus digoxin and placebo; ‡p <0.05 versus placebo.

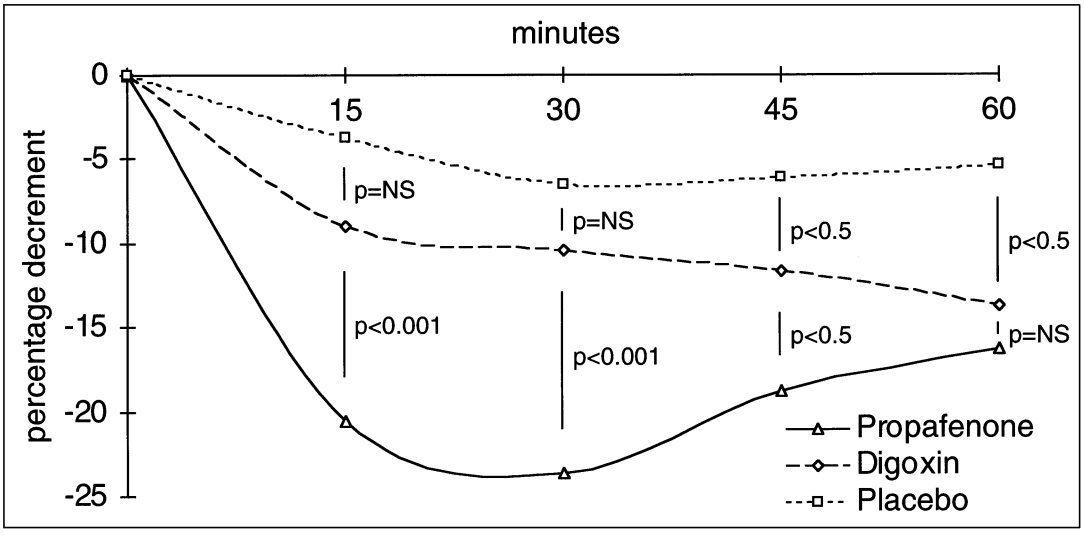

FIGURE 2. Time course of ventricular rate decrements with respect to baseline in the 3 groups of patients over the 1-hour observation time.

drawbacks. The first is that the longer atrial fibrillation lasts, the more pronounced the "electrical remodeling" may be,[23] leading to a self-maintenance of the arrhythmia and rendering its interruption more difficult. The second is related to health care costs. A prospective, observational study[24] performed in patients with atrial fibrillation or flutter treated with digoxin showed that the median time necessary to achieve a sufficient heart rate control was 12 hours, whereas 41% of the patients needed the addition of β blockers or calcium antagonists. Importantly, patients spent a median time of 4 days in the hospital, 28% of them in an intensive care unit and the rest in a telemetry bed. Based on 1991 data, the mean hospital bed cost per patient was estimated to exceed $3,000. Thus, if restoring sinus rhythm with a short intravenous infusion of a drug does not change the long-term history of the patient, it certainly allows for a rapid remission of their symptoms and a shorter hospital stay. If this method is followed, prolonged monitoring is not necessary and, in many instances, hospitalization itself can be avoided, creating an obvious and substantial impact on related costs.

Heart rate in nonconverters: The efficacy of digoxin in reducing ventricular rate during chronic atrial fibrillation has already been questioned.[25,26] In recent-onset atrial fibrillation, an intravenous digoxin dose of 0.75 mg in 10 minutes was reported to reduce heart rate by 15% at 10 minutes and by 17% at 30 minutes.[15] However, the significance of this observation is hampered by the fact that, if needed, the use of intravenous verapamil was allowed. In the Digoxin in Acute Atrial Fibrillation study,[16] the first measurement of heart rate was obtained only 2 hours after the infusion; at that time heart rate was lower in digoxin than in placebo patients.

In the present study, the ventricular rate in patients remaining in atrial fibrillation significantly decreased with respect to baseline in all 3 groups of patients, but it responded differently depending on treatment. In placebo patients, the heart rate decrease, although significant, was modest and stable over time. Propafenone, on the contrary, exerted a rapid and marked depressive effect on heart rate (−21% at 15 minutes), maximal at 30 minutes (−24%) and then slowly decreasing (−16% at 60 minutes). The effect of digoxin on heart rate was even more varied: it was slow, becoming statistically different versus placebo after 45 minutes (−12%), and having the same effect as propafenone (−14%) only 60 minutes after the start of the infusion. Actually, the drug effect on the atrioventricular node is not direct, but mediated by vagal activation, and it becomes apparent only as the high sympathetic drive associated with acute atrial fibrillation slowly subsides. In contrast, the depressant action of propafenone on the atrioventricular node is direct and remarkable, although in the absence of a drug continuous infusion, it tends to gradually decrease, probably correlating with the progressive decrease in the drug plasma concentrations.

Adverse effects: The sample size of the present study is too small to allow an assessment of the relative safety of the 2 drugs, whose favorable safety profile has already been recognized.[16,17] However, no severe side effects were observed with either drug. The only relevant untoward effect was hypotension, (transient and requiring no treatment but saline infusion), observed in 5% of propafenone patients. Mild to moderate hypotension was the most frequent side effect (3%), reported in a large safety study on propafenone involving 349 patients.[17]

Transformation of atrial fibrillation to atrial flutter may occur spontaneously[27]; this has frequently been described with class IC antiarrhythmic agents,[7,9,27,28] which, by decreasing conduction, tend to "organize" the atrial electrical activity, often before arrhythmia termination. This has to be considered a consequence of the electrophysiologic action of class IC drugs rather than an untoward effect, unless the high ventricular rate due to 1:1 atrioventricular conduction occurs. This last phenomenon, reported during oral treatment with IC agents,[28–30] has not been observed in our patients, and to our knowledge, has not occurred in any trial with intravenous propafenone for atrial fibrillation.

Conclusion: A short intravenous infusion of propafenone is preferable to intravenous digoxin in patients with recent-onset atrial fibrillation, provided heart failure and excitation-conduction disturbances are excluded. In fact, it is twice as effective in rapidly restoring sinus rhythm. Whereas the digitalis effect on atrioventricular conduction is weak and slow-appearing, propafenone rapidly decreases the rapid ventricular rate associated with the arrhythmia. Although a trend toward a higher conversion rate was observed with digoxin, it was not more effective than placebo in converting patients to sinus rhythm.

APPENDIX

The Propafenone in Atrial Fibrillation Italian Trial (PAFIT) 3 Investigators: STUDY CO-ORDINATOR: Leopoldo Bianconi, MD, San Filippo Neri Hospital, Rome.

Investigators and Centers (number of included patients): Tiziano Lenzi, MD, Andrea Strada, MD, Policlinico S. Orsola, Bologna (24 patients); Enzo Venturini, MD, Sergio Sonnino, MD, Ospedale D. Parodi, Colleferro (Roma) (24 patients); Augusto Papalardo, MD, Antonio Palamara, MD, Policlinico Casilino, Roma (20 patients); Daniela Tovena, MD, Geremia Milanesi, MD, Ospedale Maggiore, Crema (Cremona) (12 patients); Roberto Turato, MD, Giovanni Ventura, MD, Ospedale Fornaroli, Magenta (Milano) (9 patients); Giuseppe Montemurro, MD, Alessandra Stifani, MD, Ospedale Del Ponte, Varese (9 patients); Giovanni Falsini, MD, Mauro Forzoni, MD, Ospedale Alberti, S. Giovanni Valdarno (Arezzo) (9 patients); Antoni Cirò, MD, Antonio Vincenti, MD, Ospedale S. Gerardo, Monza (Milano) (8 patients); Leonello Battara, MD, Nicola Rinaldi, MD, Ospedale Civile, Riccione (Rimini) (7 patients); Angelo Baroletti, MD, Alessandro Bini, MD, Ospedale Civile, Empoli (Firenze) (3 patients).

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