REVIEW ARTICLE

Oral antiarrhythmic drugs in converting recent onset atrial fibrillation

• Vera H.M. Deneer, Marieke B.I. Borgh, J. Herre Kingma, Loraine Lie-A-Huen and Jacobus R.B.J. Brouwers

Pharm World Sci 2004; 26: 66–78.

V.H.M. Deneer (correspondence, e-mail: vhm.deneer@farmacie.rhijnhuysen.net), **M.B.I. Borgh, L. Lie-A-Huen:** Department of Clinical Pharmacy
J.H. Kingma: Department of Cardiology, St Antonius Hospital, Koekoekslaan 1, 3435 CM Nieuwegein, The Netherlands
J.R.B.J. Brouwers: Groningen University Institute for Drug Exploration (GUIDE), Section of Pharmacotherapy, University of Groningen, Antonius Deusinglaan 1, 9713 AV Groningen, The Netherlands

Key words
Atrial fibrillation
Amiodarone
Antiarrhythmic drugs
Digoxin
Episodic treatment
Flecainide
Propafenone
Quinidine
Sotalol
Verapamil

Abstract
Aim: This article reviews clinical studies on oral antiarrhythmic drugs in converting recent onset atrial fibrillation. An oral loading dose of an antiarrhythmic drug for cardioversion of atrial fibrillation could be an option, due to its simplicity, both for patients admitted to outpatient departments and for episodic treatment by self administration outside the hospital. The latter treatment strategy has recently been pointed out by the American College of Cardiology, the American Heart Association and the European Society of Cardiology as the 'pill in the pocket approach'.
Methods: Articles were identified by Medline 1966 to November 2001 and Embase 1966 to November 2001. Randomized studies of oral antiarrhythmic drugs versus placebo or comparative treatment, which are written in the English language, were selected. Non-randomized or non-comparative studies were selected if the results of an analysis to identify predictors for successful conversion are described. The review of clinical trials is followed by a description of pharmacokinetic parameters of the antiarrhythmic drugs.
Results: Studies meeting the inclusion criteria were on propafenone, flecainide, sotalol, amiodarone, quinidine, digoxin and verapamil. Conversion rates of a single oral loading dose of 600 mg propafenone varied between 37% and 41% at 4 h after ingestion. Propafenone was more effective than quinidine, amiodarone and placebo. A single oral dose of 300 mg flecainide restored sinus rhythm in 59% and 68% of patients at 3 h. Flecainide was more effective than amiodarone and placebo. Oral sotalol, digoxin and verapamil were not effective in converting atrial fibrillation to sinus rhythm.
Conclusion: Propafenone and flecainide are effective in converting recent onset atrial fibrillation. No serious ventricular arrhythmia, other serious proarrhythmic effects or serious non cardiac adverse events were observed. Regular supraventricular tachyarrhythmias with 1:1 AV conduction were rare and were also observed in placebo treated patients. Propafenone and flecainide are more effective in patients with atrial fibrillation of less than 24 h. The association between cardioversion and patient characteristics are not consistent between studies. The pharmacokinetics of flecainide, with lower interindividual variability of absorption kinetics, no genetically determined formation of an active metabolite and a more rapid distribution to myocardial tissue, are more favourable for episodic treatment as compared to propafenone. Both flecainide and propafenone are safe in hospitalized patients. Out of hospital self administration of antiarrhythmic drugs, also described as the 'pill in the pocket approach', could be an option for selected patients, after the treatment has proven to be safe in hospital.

Accepted July 2003

Introduction

Atrial fibrillation is the most common arrhythmia. The incidence of atrial fibrillation depends on the age of the study population. The incidence varies between 2 or 3 new cases per 1,000 population per year between the ages of 55 and 64 years to 35 new cases per 1,000 population per year between the ages of 85 and 94 years[1]. Treatment of an episode of paroxysmal atrial fibrillation consists of restoring sinus rhythm by DC-electrical cardioversion or by the intravenous administration of an antiarrhythmic drug, but frequently the arrhythmia spontaneously terminates[1–3]. After one or more episodes of atrial fibrillation chronic prophylactic treatment with an antiarrhythmic drug is often started for maintenance of sinus rhythm[4–8]. Another treatment strategy consists of allowing the arrhythmia to exist in combination with pharmacological ventricular rate control. A single oral loading dose in restoring sinus rhythm would be more convenient than the intravenous administration of an antiarrhythmic drug. Due to its simplicity oral loading dosing could be an option both for patients admitted to outpatient departments and for episodic treatment by self administration outside the hospital[9–13]. This treatment strategy has recently been pointed out by the American College of Cardiology, the American Heart Association and the European Society of Cardiology as the 'pill in the pocket approach'[14].

Episodic treatment implies an early intervention. This seems attractive because in an animal model it was shown that within a few hours after its onset atrial fibrillation leads to electrical remodelling which enhances the persistence of atrial fibrillation[15]. An early recovery of sinus rhythm may favour the maintenance of sinus rhythm, gives an early relief of symptoms and reduces the risk of thromboembolic complications[3, 15]. Episodic on demand treatment of atrial fibrillation might be a useful alternative to chronic prophylactic treatment with antiarrhythmic drugs. It overcomes the problems of patient compliance and the occurrence of side effects necessitating to change the dosage or to discontinue the medication[4, 16–18]. Frequent DC-electrical cardioversions or acute treatment with intravenously administered antiarrhythmic drugs could also be an option in patients in whom chronic treatment is problematic. However, this treatment strategy requiring hospitalisation or admittance to emergency departments is both costly and inconvenient for patients[2].

To determine the efficacy of oral antiarrhythmic drugs in converting short lasting atrial fibrillation relevant studies are reviewed.

Methods

Published clinical trials studying oral antiarrhythmic drugs in converting atrial fibrillation are reviewed. Articles were identified by Medline 1966 to November 2001 and Embase 1966 to November 2001. Subsequently references were checked. Search terms were:

atrial fibrillation, atrial tachycardia, supraventricular arrhythmia, supraventricular tachyarrhythmias, supraventricular tachycardia, conversion, cardioversion, antiarrhythmic drugs, flecainide, propafenone, amiodarone, sotalol, quinidine, digoxin, disopyramide, verapamil, procainamide, dofetilide.

The efficacy of some intravenously administered antiarrhythmic drugs in converting atrial fibrillation was highly dependent on the time of onset of the arrhythmia. Efficacy decreased with increasing duration of atrial fibrillation[19, 20]. In episodic treatment patients are expected to take their medication shortly after the onset of the arrhythmia. Therefore, studies were only selected if patients with a duration of atrial fibrillation of less than 24 h, were allowed to be included. Studies in which oral antiarrhythmic drugs were preceded by the intravenous administration of the drug and studies on atrial fibrillation following cardiac surgery were excluded. This review includes randomized studies of oral antiarrhythmic drugs versus placebo or comparative treatment, which are written in the English language. Non-randomized or non-comparative studies were selected if the results of an analysis to identify predictors for successful conversion are described. The review of clinical trials is followed by a description of pharmacokinetic parameters of the antiarrhythmic drugs. A meta-analysis was not performed because the study populations varied widely in the duration of atrial fibrillation which highly influences the efficacy results.

Results

Efficacy

In episodic treatment and treatment at outpatient departments a rapid conversion to sinus rhythm is desirable. This gives an early relief from symptoms, prevents clot formation, prevents the occurrence of electrical remodelling and makes an early discharge from hospital possible. Therefore, conversion rates within a short time period after ingestion are especially focussed on. Mean conversion times after the ingestion of the antiarrhythmic drugs are highly dependent on the duration of the observation period and are not very useful in comparing efficacy between studies. Common exclusion criteria of the reviewed studies were: New York Heart Association functional class of ≥ 2 or > 2 or signs and symptoms of heart failure, any previous conduction disturbances other than atrial fibrillation, sick sinus syndrome, recent myocardial infarction and unstable angina. In general stable patients with only mild cardiac disease, such as hypertension, valvular heart disease and coronary artery disease, were allowed to be included.

Propafenone

Results of studies in which propafenone was used are shown in Table 1. In most studies patients were treated with a single oral loading dose of 600 mg propafenone[21–26]. In two studies a body weight adjusted dosage regimen was used[27, 28]. In all studies propafenone was administered as two or more tablets. In several studies propafenone doses were repeated at 4 to 24 h if atrial fibrillation persisted[22, 26, 27, 29, 30]. If the efficacy at time points before a second dose was reported these conversion rates were tabulated[22, 26, 27]. Conversion rates were 3%[23] and 15%[25] at 1 h, was 41% and 43% at 2 h[28, 31], varied between 45 and 55% at 3 h[21, 23, 24] and ranged from 37% to 71% at 4 h after ingestion[22, 25, 26, 31]. Propafenone was more effective than placebo at 3 to 12 h[21, 28]. However, after an observation period of 24 h the difference between propafenone and placebo disappeared and conversion rates became similar[31]. In one study, after an initial higher efficacy of propafenone, the difference between the propafenone and the placebo group disappeared at 6 h[27].

A single oral dose of 450 mg propafenone was less effective than 600 mg at 2 h, while conversion rates at 4 to 24 h were not significantly different[31]. Mean conversion times were 287 ± 352 min and 279 ± 237 min for the 600 mg dose and the lower dose respectively, while the observation period was 24 h. Propafenone was equally effective as an oral loading dose of flecainide with mean conversion times of 165 ± 119 min and 158 ± 109 min respectively and an observation period of 8 h[21]. Intravenously administered propafenone was more effective than oral propafenone at 1 h. However, at 3 and 6 h conversion rates were similar[23] with conversion times of 138 ± 140 min for intravenous propafenone and 163 ± 114 min for oral propafenone[23]. In a study of Botto et al.[25] intravenous propafenone also showed a higher conversion rate at 1 h after administration. At 4 and 8 h conversion rates of oral propafenone became higher than intravenous propafenone while at 8 h statistical significance was reached. Oral propafenone was more effective in restoring sinus rhythm than oral amiodarone at 4 h after ingestion[26]. The proportion of patients with sinus rhythm at 3 h was higher in propafenone treated patients than in patients treated with the combination of digoxin and quinidine. Conversion rates were similar at 6 h[27]. This study also showed that the addition of digoxin to propafenone increased efficacy from 50% to 75% of patients with sinus rhythm at 6 h after start of treatment[27].

Flecainide

Flecainide, like propafenone, is a class Ic antiarrhythmic drug[32]. Flecainide is available as racemic mixture. Studies in which patients were treated with flecainide are tabulated in Table 2. In 2 studies a single loading dose of 300 mg flecainide administered as 3 tablets of 100 mg each were used[21, 33]. In the most recent study a single dose of 4 mg/kg of flecainide with a maximum of 300 mg was administered as an oral solution[34]. In the study of Crijns et al.[35] patients received repeated doses of flecainide tablets up to 400 mg within 3 h.

Sinus rhythm was restored in 68% of patients at 2 h[34], in 59%[21] and 68%[33] of patients at 3 h and in 50% of patients at 5 h after (the first) ingestion of flecainide. In patients with atrial fibrillation lasting less than 24 h 71% converted within 5 h[35]. Of those patients who had sinus rhythm at 5 h 60% converted within 1 h after the first 200 mg dose[35]. Flecainide was more effective than placebo at 3 and 8 h[21, 33]. Conversion rates of oral flecainide and oral propafenone were similar[21]. From two studies it appeared that oral flecainide was equally effective as a rapid intravenous infusion of flecainide[34, 35]. It should be pointed out that in both studies the absorption of flecainide was expected to be faster as compared to the studies in which a single loading dose of flecainide tablets were used. Alp et

Table 1 *Oral propafenone*

Authors, year	*Comparison with*	*AF duration inclusion criterium*	*AF duration per group*[a]	*Total number of patients*	*Number of patients per group*	*Dose*	*Conversion rate*
Capucci et al. 1994[22]	Digoxin i.v./quinidine oral Placebo	< 8 days	P: 19 h D/Q: 22 h Pl: 20 h	87	P: 29 D/Q: 29 Pl: 29	600 mg	4 h: 62 vs 24% D/Q ($P < 0.01$) vs 10% Pl ($P < 0.001$) 6 h: 62 vs 38% D/Q (NS) vs 17% Pl ($P < 0.001$)
Capucci et al. 1994[21]	Flecainide oral Placebo	< 7 days	P: 36 h F: 34 h Pl: 35 h	181	P: 61 F: 58 Pl: 62	600 mg	3 h: 51 vs 59% F (NS) vs 18% Pl ($P < 0.001$) 8 h: 72 vs 78% F (NS) vs 39% Pl ($P < 0.001$)
Weiner et al. 1994[30]	Verapamil oral	< 2 weeks	60% < 24 h	46	P: 24 V: 22	150 mg every 4 h up to 48 h	12 h: 42 vs 14% V (NS) 24 h: 79 vs 27% V(NA) 48 h: 88 vs 41% V ($P < 0.001$)
Boriani et al. 1995[23]	Propafenone i.v. Placebo	< 7 days	P: 9 h P iv: 8 h Pl: 7 h	87	P: 29 P iv: 29 Pl: 29	600 mg	1 h: 3 vs 28% P iv ($P < 0.05$) vs 3% Pl (NS) 3 h: 55 vs 41% P iv (NS) vs 10% Pl ($P < 0.001$) 8 h: 69 vs 66% P iv (NS) vs 24% Pl ($P < 0.005$)
Boriani et al. 1997[24]	Placebo	< 7 days	P: 31 h Pl: 30 h	240	P: 119 Pl: 121	600 mg	3 h: 45 vs 18% Pl ($P < 0.001$) vs 37% Pl ($P < 0.001$)
Botto et al. 1997[31]	Placebo Propafenone 450 mg (low dose) oral	< 3 days	P: 1.5 days P: 1.7 days (low dose) Pl: 1.4 days	105	P: 35 P low dose: 35 Pl: 35	600 mg	2 h: 43 vs 8% low dose ($P = 0.001$) vs 11% Pl ($P = 0.004$) 4 h: 57 vs 46% low dose (NS) vs 17% Pl ($P < 0.001$) 8 h: 69 vs 63% low dose (NS) vs 34% Pl ($P < 0.01$) 24 h: 80 vs 71% low dose (NS) vs 69% Pl (NS)

Table 1 *Continued*

Authors, year	*Comparison with*	*AF duration inclusion criterium*	*AF duration per group*[a]	*Total number of patients*	*Number of patients per group*	*Dose*	*Conversion rate*
Azpitarte et al. 1997[28]	Placebo	< 1 week	P: 22.7 h Pl: 18.0 h	55	P: 29 Pl: 26	450 mg if 51–64 kg 600 mg if 65–85 kg 750 mg if > 85 kg	2 h: 41 vs 8% Pl ($P = 0.005$) 6 h: 65 vs 31% Pl ($P = 0.015$) 12 h: 69 vs 42% Pl ($P = 0.060$) 24 h: 79 vs 73% Pl (NS)
Di Benedetto et al. 1997[29]	Digoxin i.v./quinidine oral	< 6 months	72% ≥ 8 days	50	P: 25 D/Q: 25	600 mg 300 mg after 6 h and than 300 mg after 8 h	18 h for D/Q and 22 h for P 28 vs 84% D/Q ($P < 0.001$)
Botto et al. 1998[25]	Propafenone i.v. Placebo	< 3 days	P: 11 h P iv: 17 h Pl: 15 h	123	P: 41 P iv: 40 Pl: 42	600 mg	1 h: 15 vs 48% P iv ($P < 0.005$) vs 17% Pl (NS) 4 h: 71 vs 50% P iv (NS) vs 33% Pl ($P = 0.001$) 8 h: 78 vs 53% P iv ($P < 0.03$) vs 48% Pl ($P < 0.01$)
Capucci et al. 1999[27]	Digoxin i.v./quinidine oral Digoxin iv/propafenone oral Placebo	< 2 days	P: 17.8 h D/Q: 14.7 h D/P: 16.0 h Pl: 13.0 h	246	P: 66 D/Q: 70 D/P: 70 Pl: 40	< 60 kg: 450 mg > 60 kg: 600 mg	conversion rate: NR mean ± SD conversion times with an observation period of 24 h: 4.0 ± 4.1 vs 5.0 ± 8.6 h D/P (NS) vs 5.4 ± 4.5 h D/Q (NS) vs 7.8 ± 7.2 h Pl ($P < 0.01$)
Blanc et al. 1999[26]	Amiodarone oral	< 2 weeks	P: 1 day A: 1 day	86	P: 43 A: 43	600 mg	4 h: 37 vs 16% ($P < 0.05$) 24 h: 56 vs 47% (NS)

AF – atrial fibrillation, A – amiodarone, D/P – combination of digoxin and propafenone, D/Q – combination of digoxin and quinidine, F – flecainide, P – propafenone, Pl – placebo, NA – not analysed, NR – not reported, NS – not statistically significant, *P* – *P*-value obtained in statistical analysis, vs – versus.
[a] Mean values unless stated otherwise.

al.[34] randomized patients to intravenous flecainide or an oral solution of flecainide. In healthy subjects the absorption of flecainide administered as an oral solution was faster as compared to a tablet[12]. In the second study a rapid absorption profile was obtained by ingesting multiple tablets of flecainide within a short time period[35].

Sotalol

Only one study on oral sotalol in which patients with recent-onset atrial fibrillation were allowed to be included, has been published[36]. Sotalol is available as racemic mixture. Patients were randomized to multiple doses of 80 mg sotalol tablets or the combination of digoxin and quinidine (Table 3). In the sotalol group first an 80 mg dose was given. This dose was repeated after 2, 6 or 10 h if atrial fibrillation persisted and if heart rate and blood pressure allowed this. In the digoxin/quinidine group, initially digoxin was given intravenously until heart rate was approximately 100 beats/min or until 0.75 mg of digoxin was given. Subsequently, 200 mg of quinidine was given maximally 3 times 2 h apart or until cardioversion to sinus rhythm occurred. After ingestion of the first 80 mg dose in only 12% of patients sinus rhythm was restored at 2 h. At 3 h 12% of patients in the sotalol group versus 36% in the digoxin/quinidine group had converted. At 8 h conversion rates for the sotalol and digoxin/quinidine group were 24% versus 71%, while 12 h after the last dose conversion rates were 52% and 86%, respectively. Statistical analysis was only performed on the last conversion rates and the difference of both treatment groups was significantly different. After an interim analysis the study was interrupted because of the low efficacy of sotalol. The authors concluded that the efficacy of sotalol in their study was similar to the efficacy of placebo in the study of Capucci et al.[21].

Amiodarone

One randomized study in which patients were treated with oral amiodarone has been published[26]. Amiodarone was administered orally at a dose of 30 mg/kg, meaning that 10 to 12 tablets were ingested over 2 to 3 min. Oral amiodarone was compared with oral propafenone (Table 1). At 4 h in 16% of patients treated with oral amiodarone sinus rhythm was restored and amiodarone was less effective than propafenone, with a conversion rate of 37%. However, at 24 h conversion rates were similar. The median time for restoration of sinus rhythm was shorter in the propafenone group than in the amiodarone group being 2.4 h (range 0.05–20.5 h) and 6.9 h (range 0.05–19.5 h) ($P = 0.05$), respectively.

Quinidine

Studies on quinidine are shown in Table 3. Quinidine was administered in repeated doses every 2 or 3 h until conversion or up to a total dose of 600 to 1500 mg[22, 27, 30, 36]. No single dose studies were performed in patients with recent onset atrial fibrillation. In all studies digoxin was used for ventricular rate control. In the study of Capucci et al.[22] quinidine was not started until six hours after the first digoxin dose. At 6 h 38% of patients had converted to sinus rhythm. Conversion rates at 12, 24 and 48 h were 48%, 76% and 79% respectively. No significant differences were found in the conversion rates and conversion times between the digoxin plus quinidine group and the placebo group. Mean conversion times within 48 h were 648 ± 631 min for digoxin plus quinidine and 893 ± 622 min for placebo. At 12 h digoxin plus quinidine was less effective than propafenone 600 mg followed after 8 h by 300 mg 3 times daily. In another study, quinidine was started at 1 h after the first dose of digoxin. Conversion rates and times of conversion were not significantly different from placebo at 3 and 6 h[27]. The combination of digoxin and quinidine was less effective than propafenone at 3 h[27] and more effective than sotalol[36]. In the study of Di Benedetto et al.[29] both patients in the propafenone and quinidine group were digitalized. Sinus rhythm was restored in 84% of the patients treated with quinidine. Quinidine was more effective than propafenone, which was effective in only 28% of patients. The time point at which conversion rates were assessed was not reported. However, the last dose of propafenone was given at 14 h and at 15 h in case of quinidine. The low conversion rate in the propafenone group was in contrast to the results of other studies (Table 1). However, the study population of Di Benedetto et al.[29] was different with respect to the duration of atrial fibrillation. The majority of patients had the arrhythmia for more than eight days.

Other antiarrhythmic drugs

Falk et al.[37] randomized 36 patients with atrial fibrillation of less than 7 days to digoxin or placebo. Digoxin solution in capsules were given in doses of 0.6, 0.4, 0.2 and 0.2 mg at 0, 4, 8 and 14 h or until cardioversion. Conversion rates and times to conversion of both groups were similar. Nine of eighteen patients (fifty percent) receiving digoxin and eight of eighteen patients (forty-four percent) receiving placebo converted to sinus rhythm. Mean time to conversion was 5.1 h in the digoxin group and 3.3 h in the placebo group. Oral dofetilide has been studied in patients with heart failure and left ventricular dysfunction with an endpoint of 30 days after start of treatment[38] and in patients with long lasting atrial fibrillation[39]. In the study of Weiner et al.[30] (Table 1) verapamil treated patients served as control group. Patients were treated with 40 mg every 4 h, up to 48 h or until conversion to sinus rhythm. Conversion rates of the verapamil and propafenone group were 14% and 42% respectively at 12 h, while at 24 h conversion rates of 27% and 79% were found and statistical significance was reached.

Predictors of successful conversion

In a non-comparative study in which patients were treated with an oral loading dose of propafenone a duration of atrial fibrillation of less than 24 h was a significant predictor of cardioversion[40]. Clinical variables such as age, gender, hypertension, congestive heart failure, mitral stenosis, coronary artery disease, diabetes mellitus and chronic obstructive lung disease were not associated with cardioversion. In contrast to the other studies reviewed, the percentage of patients with underlying cardiac disease was higher. Heart failure was not an exclusion criterium and 9 patients (18%) with heart failure were included. A higher efficacy in patients with atrial fibrillation of less than 24 h was also observed for oral flecainide[35]. In the study of Blanc et al.[26] patients with an atrial fibrillation duration of < 2 days had a significantly higher conversion rate

Table 2 *Oral flecainide*

Authors, year	*Comparison with*	*AF duration inclusion criterium*	*AF duration per group*[a]	*Total number of patients*	*Number of patients per group*	*Dose*	*Conversion rate*
Crijns et al. 1988[35]	Flecainide iv	< 6 months	68% < 24 h	40	F: 20 F iv: 20	200 mg–400 mg (200 mg, at 1 h 100 mg, at 3 h 100 mg)	AF < 24 h, efficacy at 5 h 10/14 vs 10/13 F (iv, NS) AF > 24 h, efficacy at 5 h 0/6 vs 0/7 F (iv, NS)
Capucci et al. 1992[33]	Amiodarone iv followed by oral amiodarone Placebo	< 7 days	F: 28 h A: 30 h Pl: 27 h	62	F: 22 A: 19 Pl: 21	300 mg	3 h: 68 vs 16% A ($P < 0.005$) vs 29% Pl ($P < 0.05$) 8 h: 91 vs 37% A ($P < 0.001$) vs 48% Pl ($P < 0.01$)
Capucci et al. 1994[21]	Propafenone oral Placebo	< 7 days	F: 34 h P: 36 h Pl: 35 h	181	F: 58 P: 61 Pl: 62	300 mg	3 h: 9 vs 51% P (NS) vs 18% Pl ($P < 0.001$) 8 h: 78 vs 72% P (NS) vs 39% Pl, ($P < 0.001$)
Alp et al. 2000[34]	Flecainide iv	< 48 h	F: 10.8 h F iv: 11 h	79	F: 40 F iv: 39	4 mg/kg max 300 mg	2 h: 8 vs 64% (F iv, NS) 8 h: 75 vs 72% (F iv, NS)

AF – atrial fibrillation, A – amiodarone, F – flecainide, P – propafenone, Pl – placebo, NS – not statistically significant, *P* – *P*-value obtained in statistical analysis, vs – versus.
[a] Mean values unless stated otherwise.

Table 3 *Oral quinidine*

Authors, year	*Comparison with*	*AF duration inclusion criterium*	*AF duration per group*[a]	*Total number of patients*	*Number of patients per group*	*Dose*	*Conversion rate*
Capucci et al. 1994[22]	Propafenone oral[d] Placebo	< 8 days	D/Q: 22 h P: 19 h Pl: 10 h	87	D/Q: 29 P: 29 Pl: 29	digoxin iv was followed at 6 h by quinidine[b]	6 h: 38 vs 62% P, NS vs 17% Pl 12 h: 48 vs 83% P, $P < 0.05$ vs 34%, NS 24 h: 76 vs 86% P, NS vs 55% Pl, NS 48 h: 79 vs 86% P, NS vs 76% Pl, NS
Halinen et al. 1995[36]	Sotalol oral	< 2 days	D/Q: 11.8 h S: 12.4 h	61	D/Q: 28 S: 33	digoxin iv was followed by quinidine[c]	3 h: 36 vs 12% S, NA 8 h: 71 vs 24% S, NA 18 h for D/Q and 22 h for P: 86 vs 52% S, $P < 0.01$
Di Benedetto et al. 1997[29]	Propafenone oral[e]	< 6 months	72% ≥ 8 days	50	D/Q: 25 P: 25	hydroquinidine chlorhydrate 150 mg followed by 300 mg at 1 h then 150 mg every 2 h until a total of 1500 mg	18 h for D/Q and 22 h for P: 84 vs 28% P ($P < 0.001$)
Capucci et al. 1999[27]	Propafenone oral[g] Digoxin iv/ propafenone oral[f, g] Placebo	< 2 days	D/Q: 14.7 h P: 17.8 h D/P: 16.0 h Pl: 13.0 h	246	D/Q: 70 P: 66 D/P: 70 Pl: 40	digoxin iv was followed at 1 h by quinidine[f]	conversion rate: NR mean ± SD conversion times with an observation period of 24 h: 5.4 ± 4.5 vs 5.0 ± 8.6 h D/P (NS) vs 4.0 ± 4.1 h (NS) vs 7.8 ± 7.2 h Pl (NS)

AF – atrial fibrillation, D/P – combination of digoxin and propafenone, D/Q – combination of digoxin and quinidine, P – propafenone, Pl – placebo, S – sotalol, NA – not analysed, NR – not reported, NS – not significant, *P* – *P*-value obtained in statistical analysis, vs – versus.

[a] Mean values unless stated otherwise.

[b] Intravenous digoxin was followed at 6 h by 300 mg of hydroquinidine chlorhydrate followed by 150 mg every 3 h for 9 h and then 150 mg every 8 h.

[c] Digoxin was given initially in patients with a heart rate of > 100 beats/min until a heart rate of < 100 beats/min or until a cumulative dose of 0.75 mg, whereafter 200 mg of quinidine sulfate was given maximally 3 times, each dose 2 h apart.

[d] 600 mg oral propafenone as a loading dose, followed after 8 h by 300 mg 3 times daily.

[e] 600 mg of propafenone followed by 300 mg after 6 h and 300 mg after 8 h; patients of both treatment groups were digitalized.

[f] If > 60 kg a total maximum digoxin dose of 1 mg/12 h, if < 60 kg a total maximum dose of 0.75 mg/12 h; a total of 1100 mg quinidine polygalacturonate was administered in 4 equal doses of 275 mg every 2 h.

[g] If > 60 kg 600 mg propafenone followed by 300 mg at 6 h, if < 60 kg the starting dose was 450 mg.

than those with a longer duration being 84% and 45% respectively.

The association between cardioversion and patient characteristics are not consistent between studies. Boriani et al.[24, 41] randomized patients to an oral loading dose of propafenone or placebo. The results were described in two separate articles. The data were analysed according to the presence of heart disease, including hypertension[24], and according to patients' age[41]. In a multivariate analysis propafenone treatment and age $\leq$ 60 years increased the probability of cardioversion at 3 and 8 h[41]. In the placebo group the conversion rate after 8 hours of patients aged $\leq$ 60 years being 46% was higher than the conversion rate of 29% for patients aged $>$ 60 years[41]. Three subgroups of patients were identified, i.e., patients without heart disease, patients with systemic hypertension and patients with structural heart disease such as coronary heart disease, valvular heart disease, cardiomyopathy or congenital heart disease. Conversion rates at 8 h for patients receiving propafenone were similar among the three groups, but conversion rates for patients receiving placebo differed significantly. Conversion rates in the placebo group were 56% for patients without heart disease, 27% for patients with systemic hypertension and 17% for patients with chronic heart disease[24]. This study demonstrates that only spontaneous conversion rates depend on patient characteristics. On the contrary, in the study of Blanc et al.[26] in which patients were randomized to receive oral propafenone or oral amiodarone the conversion rate was higher in patients with lone atrial fibrillation (78%) than in those with a cardiovascular history, i.e., hypertension and previous myocardial infarction (50%). In the study of Crijns et al.[35] on flecainide, the lower efficacy could not be explained by lower plasma concentrations or less increase in QRS duration.

In conclusion, a short duration of atrial fibrillation (i.e., $<$ 24–48 h) has consistently been identified as a predictor of successful conversion. A younger age (i.e., $\leq$ 60 years) and no underlying cardiac disease has occasionally been associated with cardioversion.

Electrocardiographic changes

The effects of antiarrhythmic drugs on electrocardiographic parameters are not reported in all studies which met the criteria for inclusion in this study.

Propafenone

For propafenone only electrocardiographic changes after a single dose are described. Mean heart rates obtained from pooled data of both patients with atrial fibrillation and sinus rhythm were excluded.

Heart rates in patients without sinus rhythm were significantly decreased from baseline at 3 to 6 h after oral propafenone[27, 31]. A single dose of 450 or 600 mg reduced the ventricular rate from baseline by 19% and 30% respectively. The change in heart rate was significantly higher as compared to placebo with a reduction of 7%[31]. In patients treated with 600 mg of oral propafenone QRS intervals immediately after conversion were longer as compared to placebo treated patients with QRS intervals of 87 ± 12 ms and 77 ± 12 ms respectively. In another study QRS intervals at 3 and 6 h after body weight adjusted dose of propafenone were significantly longer as compared to placebo[27]. A mean lengthening of QRS interval of 21% was measured immediately after conversion to sinus rhythm[21]. PR intervals being 152 ± 27 ms after placebo were significantly longer in patients treated with oral propafenone with intervals of 176 ± 32 ms. Since only intervals after cardioversion are reported these values are not necessarily maximum values[23].

Flecainide

Oral flecainide in dosages as reported in Table 2 increased QRS intervals by 20% to 30% from baseline[21, 33–35]. The measured increases of QRS intervals are most likely not maximum increases since QRS intervals were obtained at a single time point or immediately after conversion. Before conversion there were no differences in mean or maximal heart rates of patients treated with oral flecainide and placebo[33].

Quinidine

In the digoxin/quinidine group of the study of Capucci et al.[27] the QTc interval became significantly longer than placebo from the sixth hour of treatment. In an other study QTc intervals of converters were compared. QTc intervals of patients treated with the combination of digoxin and quinidine were 408 ± 34 ms *versus* 388 ± 58 ms of placebo treated patients. However, the difference did not reach statistical significance[22].

Digoxin

The mean heart rates in the 15 min before conversion of the digoxin and placebo group of the study of Falk et al.[37] were similar. Statistically significant lowering of baseline heart rate did not occur until 5.5 h after administration of digoxin.

Adverse effects

Main adverse effects are tabulated in Table 4. Phases of atrial flutter and atrial tachycardia were observed in 3% to 20% of patients treated with propafenone[21, 23, 24, 27, 28, 31, 40]. These supraventricular tachyarrhythmias often developed before conversion to sinus rhythm[21–23, 27, 28, 33, 40]. Episodes of regular supraventricular arrhythmia also occurred in 2% to 4% of placebo treated patients[21–25, 28, 31, 33]. Atrial flutter or atrial tachycardia with 1:1 AV conduction were rare and were not observed in all studies. One placebo treated patient (3%) in the study of Botto et al.[31] showed 1:1 AV conduction. In the study of Azpirtate et al.[28] 1:1 AV conduction with a ventricular rate of 250 beats/min was observed in a placebo treated patient and was controlled by adenosine. In one patient (1%) included in the study of Boriani et al.[24] and randomized to placebo AV conduction was 1:1 with a heart rate of 240 beats/min. This patient collapsed. Asymptomatic pauses lasting longer than 2 s were seen in 1% to 3% of patients receiving propafenone and in 2% to 5% of patients receiving placebo[21–24, 33]. Pauses often occurred at the time of conversion[21–23, 33]. Other adverse events associated with propafenone were: in 2% to 8% of patients QRS intervals of more than 120 ms[21, 22, 24], in 2% to 5% of patients transient complete left bundle branch block [21, 23, 27] in 2% to 10% of patients transient hypotension[21–24, 28], in 1% and 3% slight hypotension and bradycardia[22, 24], in 2% and 5% of patients junctional rhythm after conversion[21, 25], in 1 of 43 patients (2%) a non sustained ventricular tachycardia[26], in 9%

of patients mild non cardiac side effects such as headache, paresthesia, gastrointestinal disturbances[27] and in 3% of patients a reversible asymptomatic Wenckebach II degree sinus atrial block (pauses < 3 s) at the time of cardioversion[27]. Adverse effects occurred regardless of heart disease, age or other patient characteristics[24, 41–43]. Severe hypotension, responding to rapid saline infusion, occurred in 3 of 50 patients (6%) between 1 and 4 h after ingestion of a 600 mg propafenone dose[40]. In this non-randomized prospective study, the percentage of patients with underlying cardiac disease, e.g., coronary artery disease (56%) was high. In contrast to the other studies, patients with heart failure (18%) were included[40]. One patient in the study of Azpirtate et al.[28] developed sustained hypotension after a first 300 mg propafenone dose. The patient needed volume infusion and electrical cardioversion. Echocardiographic examination showed left ventricular dysfunction.

Flecainide, like propafenone a class Ic antiarrhythmic drug, has also been associated with regular supraventricular tachyarrhythmias. Phases of atrial flutter before cardioversion were detected in 3% to 9% of patients[21, 33, 34]. In 1 study 2 patients (3%) showed 1:1 AV conduction with a ventricular rate between 250 and 260 beats/min[21]. Pauses of ≥ 2 s were observed at the time of conversion to sinus rhythm in 8% and 9% of flecainide treated patients[21, 33]. Furthermore, in the study of Capucci et al.[21] 1 patient (2%) with coronary artery disease had pulmonary edema, one patient (2%) complained of transient visual blurring and one patient (2%) had a period of junctional rhythm after cardioversion. In another study of Capucci et al.[33] mild light-headedness was reported in one patient (5%). Crijns et al[35] reported the development of mild congestive heart failure which could be treated easily with diuretics in two patients (10%). Echocardiography was not performed before inclusion in the study. Therefore, patients with subclinical left ventricular impairment were missed.

In patients treated with the combination of digoxin and quinidine asymptomatic phases of atrial flutter were observed in 1 patient (3%) *versus* 4 patients (14%) in the placebo group[22]. Asymptomatic episodes of atrial flutter were detected immediately before sinus rhythm restoration in nine patients (13%) of the digoxin/quinidine group versus three patients (8%) of the placebo group[27]. An asymptomatic pause of ≥ 2 s occurred in 1 patient (3%) who received digoxin/quinidine and in 1 placebo treated patient (3%)[22]. Other adverse effects of the combination of digoxin and quinidine were: asymptomatic ventricular runs of 3 or 4 ventricular ectopic beats in one patient (1%)[27], one patient (3%) developed nausea and vomiting requiring discontinuation of the treatment[22], a complete left bundle branch block in 2 patients (3%)[27], reversible asymptomatic Wenckebach II degree sinus atrial block with pauses < 3 s at the time of conversion in 2 patients (3%), transient mild arterial hypotension was detected in 1 patient (1%), 5 patients (7%) had gastro-enteric disturbances, 2 patients (3%) complained about sickness, 1 patient (1%) had a headache and 1 patient (1%) developed dizziness[27].

In the study of Blanc et al.[26] one of 43 patients (2%) in the oral amiodarone group developed nonsustained ventricular tachycardia and in one patient (2%) supraventricular tachycardia was observed. In the study of Halinen et al.[36] oral sotalol and the combination of digoxin/quinidine were compared. Four of thirty-three patients (thirteen percent of those with ambulatory recordings) in the sotalol group and seven of twenty-eight patients (twenty-seven percent of those with ambulatory recordings) in the digoxin/quinidine group had asymptomatic wide complex tachycardia with ≥ 3 consecutive QRS complexes of > 120 ms. The longest runs were 4 and 11 consecutive beats and the fastest heart rates were 168 and 264 beats/min in the sotalol and digoxin/quinidine group, respectively. The asymptomatic longest RR interval was 6.4 s in the sotalol and 3.8 s in the digoxin/quinidine group. Two patients (nine percent) who received multiple doses of verapamil developed heart failure[30].

Pharmacokinetics

Oral antiarrhythmic drugs that are considered for episodic treatment should give a rapid loading of the effect compartment, i.e., the atria. The drug should be rapidly absorbed from the gastrointestinal tract. Intra- and interindividual variability of maximum plasma concentrations after ingestion should be low to reduce the risk of the occurrence of low ineffective concentrations or unexpectedly high concentrations associated with toxicity. The absorption of the antiarrhythmic drug might be influenced by the arrhythmia. The absorption of verapamil was delayed during an episode of supraventricular tachycardia due to gastric hypomotility[44]. The rate at which the drug distributes from the blood compartment to the atrial tissue depends on the molecular characteristics and should be high. Very little information is available about the pharmacokinetics of antiarrhythmic drugs during atrial fibrillation and the relationship between concentrations or pharmacokinetic parameters and efficacy or the occurrence of side effects. In only two studies on converting atrial fibrillation with antiarrhythmic drugs serum or plasma concentrations were determined[22, 35]. As part of two other studies, which did not meet the criteria for inclusion, serum or plasma concentrations were measured. Disopyramide serum concentrations were determined in 15 randomly selected patients who participated in a noncomparative study. Patients with atrial fibrillation were treated with 200 mg disopyramide every 4 to 6 h until cardioversion or a maximal daily dose of 800 mg. This regimen was repeated if atrial fibrillation persisted. Within 4 h mean serum concentrations within the therapeutic range (2.0–7.5 mg/l) were reached and were remained throughout the study period. No correlation between disopyramide serum concentrations and efficacy in restoring sinus rhythm was found[45]. Patients with a median duration of atrial fibrillation of 53 months were, in anticipation of electrical cardioversion, treated with a daily dose of 600 mg amiodarone for 4 weeks. During this time period 18% of patients converted to sinus rhythm. Multivariate analysis revealed that desethylamiodarone plasma levels was an independent predictor of conversion[46].

As a measure of interindividual variability coefficients of variances were calculated from published data.

Propafenone

In healthy subjects a single oral dose of 300 mg of propafenone resulted in an interindividual variability of 60% for maximum propafenone plasma concentra-

tions. Mean time at which maximum concentrations were reached was 3.8 h after ingestion with an interindividual variability of 34%[47]. After oral administration propafenone is rapidly metabolized to its major metabolites, 5-hydroxy-propafenone and N-depropyl-propafenone. The antiarrhythmic effect of propafenone does not only depend on the parent compound but also on its 5-hydroxylated metabolite, which formation is dependent on CYP2D6 polymorphism [47]. In patients with an impairment in hydroxylating capacity propafenone leads to high plasma levels of propafenone with low or no detectable levels of 5-hydroxy-propafenone[48, 49]. After a single oral dose of 300 mg of propafenone maximum 5-hydroxy-propafenone concentrations showed an interindividual variability of 37% in healthy subjects who were phenotyped as extensive metabolizers[47].

After the ingestion of a single loading dose of 600 mg of propafenone for conversion of atrial fibrillation mean propafenone plasma concentrations were 0.58 ± 0.43 mg/l at 3 h[22]. In rabbits the myocardial uptake of propafenone was slow[50].

Flecainide

After a single oral dose of 150 or 200 mg flecainide administered as a tablet interindividual variability of maximum plasma concentrations ranged from 31% to 37%. Mean times after ingestion at which maximum concentrations were reached varied between 3 and 3.7 h with interindividual variability of 22% to 63%[51–53]. Flecainide is eliminated by both renal excretion of the unchanged molecule and oxidative metabolism to meta-O-dealkylated flecainide which is in part further metabolized to the lactam. Both metabolites have little activity. Flecainide metabolism is dependent on CYP2D6 polymorphism[54]. Maximum flecainide plasma concentrations obtained in subjects who were phenotyped as poor or extensive metabolizers after a single 50 mg dose of flecainide were similar[55]. In patients with atrial fibrillation who received up to 400 mg of flecainide in 3 h mean maximum plasma concentration was 0.46 ± 22 mg/l[35]. In rats flecainide appeared to distribute rapidly from plasma to heart tissue[56].

Sotalol

After administration of single doses of 80 mg, 160 mg or 320 mg sotalol interindividual variability of maximum sotalol plasma concentrations varying between 19% and 25%, was small. Mean times at which maximum concentrations were reached ranged from 2.7 to 3.1 h with interindividual variabilities of 23% to 37%[57, 58]. More than 70% of sotalol is renally excreted unchanged. No metabolites have been identified[59]. Sotalol appeared to be taken up rapidly by the ventricular myocardium in dogs[60].

Amiodarone

After a single oral dose amiodarone is slowly absorbed and the maximum plasma levels are reached in 4.5 h and interindividual variability in maximum concentrations is 36%[61]. Peak concentrations in the myocardium are reached within half an hour after administration of an intravenous bolus to dogs[62].

Quinidine

Immediate and slow release tablets of quinidine contain quinidine sulfate, quinidine bisulfate or quinidine polygalacturonate. In healthy subjects interindividual

Table 4 *Main adverse effects of oral antiarrhythmic drugs*

Authors, year	*Drug*	*Hypotension*[a]	*Pauses > 2 s*[a]	*Atrial flutter*[a]	*Other arrhythmias and conduction disturbances*[a]
Capucci et al. 1994[21]	P	1.6	1.6	6.6	4.9
Capucci et al. 1994[22]	P	6.9	–	–	3.4
Boriani et al. 1995[23]	P	3.4	3.4	6.9	3.4
Boriani et al. 1997[24]	P	4.2	0.8	6.7	5.0
Botto et al. 1998[25]	P	–	–	–	2.4
Blanc et al. 1999[26]	P	–	–	4.7	2.3
Capucci et al. 1999[27]	P	–	–	19.7	7.6
Azpitarte et al. 1997[28]	P	13.8	3.4	3.4	3.4
Weiner et al. 1994[30]	P	–	–	–	–
Botto et al. 1997[31]	P	–	–	12.9	–
Capucci et al. 1992[33]	F	–	9.1	9.1	–
Alp et al. 2000[34]	F	–	–	2.5	–
Crijns et al. 1988[35]	F	–	–	–	–
Capucci et al. 1994[21]	F	–	8.6	6.9	1.7
Capucci et al. 1994[22]	D/Q	–	3.4	3.4	–
Halinen et al. 1995[36]	D/Q	–	7.1[b]	–	25.0
Capucci et al. 1999[27]	D/Q	–	–	12.8	7.1
Halinen et al. 1995[36]	S	57.1[c]	7.1[b]	–	14.3
Blanc et al. 1999[26]	A	–	–	–	4.7
Weiner et al. 1994[30]	V	–	–	–	–

A – amiodarone, D/Q – combination of digoxin and quinidine, F – flecainide, P – propafenone, S – sotalol, V – verapamil, – = not reported.
[a] Tabulated values are percentages of patients with the adverse effect.
[b] Pauses of more than 3 s were reported.
[c] Hypotension or bradycardia.

variabilities of maximum concentrations after a single dose of 200 mg or 400 mg quinidine sulfate, administered as one or two immediate release tablets, were 21% and 33%. Maximum concentrations were reached at approximately 2 h with an interindividual variability of 36%[63, 64].

Discussion

From the reviewed studies it appears that a single oral loading dose of propafenone or flecainide is very effective in converting recent onset atrial fibrillation. This was also concluded from a retrospective analysis of several studies[65]. Oral propafenone and flecainide are especially useful in countries such as the USA where intravenous class Ic drugs are not available. Propafenone has been studied more extensively than flecainide. However, flecainide has more favourable pharmacokinetics than propafenone. The absorption kinetics of flecainide has a low interindividual variability in contrast to propafenone. Furthermore, the antiarrhythmic effect of propafenone depends in part on an active metabolite. The extent to which this metabolite is formed is genetically determined.

Electrical cardioversion remains indicated in patients with atrial fibrillation with acute hemodynamic instability. Anticoagulation therapy before electrical and pharmacological cardioversion is an issue because of the risk of embolization of intracardiac thrombi upon conversion. In some studies patients with atrial fibrillation for more than 24 to 72 h without long term anticoagulant treatment were excluded[21, 23, 24, 35, 41, 65]. In other studies patients were heparinized[26, 34], received low molecular weight heparin[34, 40] or transesophageal echocardiography was performed to exclude thrombi[26]. From the reviewed studies no data were available regarding treatment after cardioversion.

The safety of oral loading dosing of antiarrhythmic drugs by self administration outside the hospital remains an issue. Antiarrhythmic drugs have been associated with proarrhythmia[14]. The occurrence of sustained monomorphic and polymorphic ventricular tachycardia has been associated with the use of class Ic antiarrhythmic drugs[32] like flecainide and propafenone[14, 66]. However, these proarrhythmias are rare in patients without structural heart disease, without conduction disturbances and with normal left ventricular function[67]. Class Ic drugs can induce life threatening arrhythmia in patients with the Brugada syndrome, a very rare cardiac disease due to mutations in ion channel genes[68, 69]. No serious ventricular arrhythmia or other serious adverse events have been observed in the single oral loading dose studies with flecainide and propafenone. All studies reviewed included hospitalized patients. Although not described in all cases, patients most likely were at rest during the study period. The majority of patients probably were in bed. Furthermore, it should be considered that patients with serious cardiac disease or previous conduction disturbances were excluded from participation in the studies.

Episodes of atrial flutter or atrial tachycardia with 1:1 AV conduction and symptomatic hypotension were rare. These side effects were also observed after intravenous administration or chronic treatment with class Ic drugs[35, 70, 71]. However, periods of supraventricular tachyarrhythmias have been detected before cardioversion to sinus rhythm in placebo treated patients. It has been suggested that this is not necessarily an effect of class Ic antiarrhythmic drugs but indicates the transition of atrial fibrillation to sinus rhythm[43]. To prevent 1:1 AV conduction the combination of class Ic antiarrhythmic drugs with a beta-blocker or calcium channel antagonist has been recommended[6, 14]. This combination has not been studied so far in the cardioversion of atrial fibrillation.

A single oral loading dose of 600 mg propafenone or 300 mg flecainide is effective and safe in converting atrial fibrillation, preferably lasting less than 24 h, to sinus rhythm in hospitalized patients. Out of hospital self administration of antiarrhythmic drugs, also described as the 'pill in the pocket approach', could be an option for selected patients[14, 72]. Patients should be hemodynamic stable during atrial fibrillation, should have no heart disease, should have no history of sinus node or AV node dysfunction or other conduction disturbances and should be without renal or hepatic impairment. Before a patient is sent home with the instruction to take a loading dose of an antiarrhythmic drug at the first symptoms of an attack of atrial fibrillation, the treatment should have been proven effective and safe in hospital. Episodic treatment has been evaluated in patients with infrequent, well-tolerated paroxysmal supraventricular tachycardia. Patients were instructed to ingest a single dose of flecainide or the combination of diltiazem and propranolol out of hospital shortly after the onset of the arrhythmia. The percentage of patients calling of emergency room assistance was significantly reduced from 100% to 9% as compared to the year before enrollment. At the end of follow-up, the majority of patients were satisfied with the treatment and it was continued[10].

Hardly any pharmacokinetic parameters are available from studies in which antiarrhythmic drugs are used for converting atrial fibrillation. For future research it is important to obtain these data to assess the relationship between pharmacokinetics and both efficacy and the development of side effects.

Conclusion

Single oral loading doses of propafenone and flecainide are effective in converting recent onset atrial fibrillation in patients without severe cardiac disease. The episodic treatment strategy with oral antiarrhythmic drugs in patients with paroxysmal atrial fibrillation has not been investigated systematically so far.

Acknowledgement

We acknowledge Janet Joosten for her assistance in preparing the manuscript.

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