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Safety of Flecainide

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Abstract

Flecainide is a class Ic antiarrhythmic agent that has an important role as part of rhythm control strategies in patients with atrial fibrillation (AF). Early clinical data on the use of flecainide showed an increase in arrhythmias and mortality compared with placebo in patients with a previous myocardial infarction and asymptomatic or mildly symptomatic ventricular arrhythmias. These findings only apply to a specific group of patients with left ventricular dysfunction and ischaemic heart disease, but had a negative impact on the use of class Ic antiarrhythmics across all indications and patient groups. The aim of this review was to evaluate the available safety data for flecainide in the literature and to assess its current use in patients with AF. Current European guidelines now recommend the use of flecainide in carefully selected groups of patients with AF who do not have structural heart disease. This includes for the cardioversion of recent-onset AF, pretreatment prior to direct current cardioversion, out-of-hospital acute oral therapy ('pill-in-the-pocket' approach) and for the ongoing maintenance of sinus rhythm. Potential cardiac adverse effects of flecainide include proarrhythmia, conduction abnormalities and negative inotropic effects. Dizziness is the most frequent non-cardiac side effect, followed by blurred vision and difficulty focusing; these are almost all mild, transient and tolerable. Data from recent clinical trials in patients with supraventricular arrhythmias suggest that flecainide has a good tolerability profile in groups of appropriately selected patients. Caution is required when using flecainide in patients with renal dysfunction, and there are a number of drug interactions, but these are well documented and manageable. Overall, flecainide is a good choice for the pharmacological management of AF. It has a good safety record and low incidence of adverse effects, rare end-organ toxicity and a low risk of ventricular proarrhythmia. To ensure that the benefits of treatment outweigh any potential risks, careful patient selection and monitoring is required.

1. Introduction

Flecainide was first approved in Europe in Germany in 1982 and is currently available in 31 countries worldwide. It decreases the maximum upstroke velocity (V_{max}), an indirect index of the fast inward sodium current (I_{Na}), and the amplitude of action potentials in atrial and ventricular muscle and in Purkinje fibres, with no effect on the resting membrane potential.[1-3] Flecainide has a high affinity for open-state sodium (Na^+) channels and markedly slows the recovery time constant of Na^+ channels during the diastole and, thus, it has been classified as a class Ic antiarrhythmic agent.[3] Flecainide-induced block of I_{Na} would be expected to increase at faster rates of stimulation ('use-dependent block') because Na^+ channels spend more time in the activated state and the diastolic time between pulses for recovery from drug-induced block is shortened. Steady-state Na^+ channel block also increases, particularly in partially depolarized than in normally polarized cardiac issues ('voltage-dependent block'), as recovery from blockade proceeds more slowly in depolarized tissues. Flecainide prolongs the action potential duration (APD) in ventricular and atrial muscle fibres, probably due to blockade of the rapid component of the delayed rectifier current (I_{Kr}), but shortens the APD in Purkinje fibres, an effect consistent with Na^+ channel blockade.[1,2,4] However, because flecainide exhibits very slow unbinding kinetics from Na^+ channels during the diastole, it prolongs refractoriness to a greater extent during the APD (i.e. post-repolarization refractoriness), decreases excitability and slows intracardiac conduction throughout the heart, even at normal heart rates in all cardiac tissues.[2,3]

For specific patient groups, class Ic antiarrhythmics are the most potent agents available to stabilize atrial rhythm. Patients with significantly

impaired left ventricular (LV) function are most likely to benefit; however, it was initially suggested that the depressant effects of flecainide on ventricular function may become clinically significant in this patient population.[5] Such a group of patients was enrolled in the CAST (Cardiac Arrhythmia Suppression Trial), which was conducted in the late 1980s.[6,7] The results of CAST are discussed in more detail in section 4 of this article. Although the results of CAST should not be generalized to other patient populations because the findings only relate to patients with LV dysfunction and ischaemic heart disease,[8] the CAST trial had a negative impact on the use of class I antiarrhythmics across all indications.[8,9] Nevertheless, flecainide has an important therapeutic role and a good benefit : risk ratio in carefully selected patients with paroxysmal or persistent atrial fibrillation (AF).[8,10-12]

The aim of this review was to evaluate the available safety data for flecainide in the literature, and to assess its current use in patients with AF. Relevant publications were identified in a MEDLINE search using the following keywords: flecainide, safety, adverse events, proarrhythmia. Additional references were identified by searching the reference lists of included papers.

2. Pharmacokinetics

Flecainide is readily absorbed after oral administration (bioavailability ~90%), reaching peak plasma levels within 2–3 hours and steady state levels within 3–5 days.[2,3,13-17] Rate and extent of absorption are not significantly affected by food or antacids.[17] Flecainide poorly binds to plasma proteins (40–50%), so it is unlikely that it displaces other protein-bound drugs to a great extent,[2,3] and is widely distributed (volume of distribution 5.5–10 L/kg), reaching much higher levels in cardiac tissues than in plasma.[14] Hence, haemodialysis removes only about 1% of an oral dose as unchanged drug. Flecainide undergoes hepatic biotransformation via cytochrome P450 (CYP) 2D6 to form two major metabolites, meta-O-dealkylated flecainide (20–50% as potent as flecainide) and the inactive meta-O-dealkylated lactam of flecainide.[14,18,19] However, after multiple doses, free (unconjugated) plasma concentrations of both metabolites are so low (<0.05 μg/mL) that is unlikely that they would contribute to the antiarrhythmic effects of the agent.[14] Flecainide and its metabolites are excreted mostly (85%) in urine, with only 5% excreted in faeces.[14,19] Approximately 30% (range, 10–50%) of the dose of flecainide is excreted unchanged in urine, mainly by glomerular filtration, while its metabolites are excreted in urine principally as conjugates.[2,14,19,20] Therefore, CYP2D6 factors, such as wide inter-individual variation in enzyme activity,[21] and drug interactions via this mechanism are unlikely to be clinically significant. Even so, a CYP2D6 interaction could become clinically relevant in patients with renal dysfunction.[9] Age-related decline in flecainide metabolism has been documented in patients with poor CYP2D6-mediated metabolism (based on CYP2D6 genotype) because metabolism was taken over by CYP1A2, whose activity decreases with age.[22]

In patients with premature ventricular contractions (PVCs) after multiple oral doses, mean plasma half-life is 20 hours (range: 12–27 hours) and the apparent clearance is 7.3 mL/min/kg (range: 4.7–11.7 mL/min/kg).[2,13-16,19] Renal clearance of flecainide decreases and its elimination half-life increases in patients with congestive heart failure or with moderate renal or hepatic impairment.[2,3,14,23] Thus, if used, lower maintenance dosages and ECG monitoring may be necessary in these patients. Renal clearance of unchanged flecainide decreases when urine is very alkaline (pH 8 or higher).[24] Thus, acidification of urine promotes drug excretion and may be beneficial in overdose cases.

The half-life of flecainide in newborns may be as long as 29 hours, decreasing to 11–12 hours in infants and 8 hours in children.[2] Because in infants with supraventricular tachycardia milk may inhibit the absorption of flecainide,[25,26] higher doses of the agent are required to achieve arrhythmia suppression in infants receiving milk feeds, and a reduction in drug dosage should be implemented when milk feeding ceases.[25,26] Patients up to 80 years of age are safely treated with usual dosages.

Over the therapeutic range, plasma levels of flecainide are approximately dose proportional. The plasma levels of flecainide correlate reasonably

well with the QRS prolongation and antiarrhythmic effects of the drug.[14] Therapeutic trough plasma levels in patients successfully treated for recurrent ventricular tachycardia (VT) range between 0.2 and 1.0 mg/mL.[13-16,27] Trough plasma levels >0.7–1 μg/mL are associated with a higher rate of cardiac adverse effects such as conduction defects or bradycardia. Periodic monitoring of plasma levels is required in patients with severe renal failure or severe hepatic disease, since elimination of flecainide from plasma may be markedly slower and is strongly recommended in patients treated with amiodarone or with moderate renal disease.

3. Current Use

Flecainide is licensed in 31 countries, including for example the US and the UK, numerous countries in Europe, Japan, South Africa, New Zealand, Australia and several South American countries. The drug is indicated in patients without structural heart disease for the prevention of (i) paroxysmal supraventricular tachycardias (PSVT), including atrioventricular (AV) nodal re-entrant tachycardia, AV re-entrant tachycardia and other supraventricular tachycardias; (ii) paroxysmal atrial fibrillation/flutter; and (iii) sustained life-threatening VT.[28] Because of its proarrhythmic risks, the use of flecainide in patients with sustained VT should be initiated in hospital and only when the benefits of treatment outweigh the risks.[28] Additionally, flecainide may produce ST elevation in lead V1; this is a characteristic of Brugada syndrome and has been used as a diagnostic tool in patients suspected of having this syndrome.[29]

The latest guidelines on the management of AF were published on behalf of the European Society of Cardiology (ESC) in 2010.[12] Rhythm control is an important part of treating AF, particularly in severely compromised patients, in those who remain symptomatic despite adequate rate control, or in whom rhythm control therapy is pursued. In addition, successful use of a particular antiarrhythmic for cardioversion may provide information on which agent to use prophylactically.[12] Recommendations for the use of class Ic antiarrhythmics, including flecainide, in patients with AF are detailed in table I.

3.1 Cardioversion of Recent-Onset Atrial Fibrillation

According to previous observations made in PVC therapy, in order to obtain an efficacious result in AF conversion, bolus administration should immediately be followed by continuous infusion (0.007 mg/kg/min) to reach optimal efficacy at 2–3 hours.[30,31] In haemodynamically stable patients with acute-onset AF (less than 48 hours duration) and preserved LV function, flecainide is one of the most efficacious and fastest drugs to restore the normal sinus rhythm (SR).[12,32,33]

Although antiarrhythmic drug therapy is associated with a lower SR conversion rate than direct current cardioversion (DCC), it is a more straightforward procedure because it does not

Table I. Recommendations for rhythm control with class Ic antiarrhythmics in patients with AF[12]

Recommendation	Class/level of evidence	Dosage
When pharmacological cardioversion is preferred and no structural heart disease is present, IV flecainide or propafenone is recommended for acute cardioversion of recent-onset AF	I/A	Flecainide: 2 mg/kg IV given over 10 min Propafenone: 2 mg/kg IV over 10 min
Pre-treatment with flecainide or propafenone should be considered to enhance the success of DCC and prevent recurrent AF	IIa/B	
Flecainide is recommended for ongoing rhythm control in patients with AF without structural heart disease	I/A	Flecainide: 200–400 mg/day PO bid Flecainide XL: 200 mg/day PO od
Based on limited evidence, oral flecainide or propafenone can be used out-of-hospital for the conversion of AF to sinus rhythm in carefully selected patients with recurrent AF ('pill-in-the-pocket' approach)	IIa/B	Flecainide: 200–300 mg PO Propafenone: 450–600 mg PO

AF = atrial fibrillation; **bid** = twice daily; **class** = class of recommendation; **DCC** = direct current cardioversion; **IV** = intravenous; **od** = once daily; **PO** = orally; **XL** = extended release.

require sedation or anaesthesia.[12] Flecainide is recommended for cardioversion of recent-onset AF (table I). A pooled analysis by the US Agency for Healthcare Research and Quality, which comprised a total of 46 clinical studies on antiarrhythmic drugs for cardioversion, showed that in haemodynamically stable patients with recent onset AF (less than 48 hours duration) and preserved LV function, acute treatment with flecainide was associated with conversion rates of between 52% and 95% and was the quickest and most efficacious drug evaluated to restore normal SR.[33] Moreover, a single-blind, randomized, comparative study showed that flecainide was significantly more effective than propafenone and amiodarone for conversion of acute AF to SR (90% vs 72% and 64%, p = 0.008).[34] A review that analysed seven placebo-controlled studies reported the efficacy of a single oral dose (300 mg) of flecainide for cardioversion of recent-onset AF; results ranged from 57% to 68% at 2–4 hours and 75% to 91% at 6–8 hours after drug administration.[35] Flecainide is equally effective via the oral or intravenous route, but a response usually occurs within 3 hours after oral administration and 1 hour after intravenous administration.[36-38] In addition, strong evidence supports pretreatment with flecainide prior to DCC to enhance the success rate and prevent early recurrence of AF.[12,39] Flecainide is not recommended for use in patients with persistent AF.[12] Additionally, flecainide is a safe and effective agent for the termination of AF in patients with Wolff-Parkinson-White syndrome. By reducing safety of conduction over the accessory pathway, flecainide blocks conduction and slows ventricular rate.[40,41]

3.2 'Pill-in-the-Pocket' Approach

Flecainide is usually initiated in a hospital setting. However, more recently, outpatient administration of an oral loading dose of flecainide has emerged as an option in patients with infrequent (e.g. between one per month to one per year) recurrences of AF.[12] However, this strategy is only suitable for highly selected patients: the episode has to be of recent onset (within 48 hours) in a patient with normal QRS duration and of good LV function without sinoatrial (SA) or AV nodal dysfunction, bundle-branch block, QT-interval prolongation, structural cardiomyopathy or Brugada syndrome.

In a pivotal clinical trial, a single oral dose of flecainide (200–300 mg) or propafenone (450–600 mg) was administered outside the hospital setting to achieve rhythm control of recent-onset AF in patients without severe heart disease who were experiencing infrequent, well tolerated arrhythmic episodes.[42] 534 episodes of AF were successfully converted to SR (success rate 94%) and the mean time to resolution of symptoms was 113 minutes. Adverse events occurred in 12 patients (7%) and consisted of non-cardiac events in 11 patients and atrial flutter with rapid ventricular rate in one.[42] Only patients for whom oral flecainide or oral propafenone as single-dose therapy for conversion of AF to SR was successful and well tolerated in the hospital setting were eligible to use out-of-hospital oral self-medication within 5 minutes of the onset of any subsequent palpitations.[42] The importance of such careful patient selection is reinforced in the ESC guidelines, which state that to successfully implement the 'pill-in-the-pocket' approach, patients need to be thoroughly screened for indications and contraindications and the efficacy and safety of oral flecainide treatment needs to have been confirmed in the hospital setting.[12] It is important to note that the ability to tolerate intravenous flecainide in hospital does not predict tolerability of out-of-hospital oral therapy and that intravenous drug administration is not appropriate as a screening tool to select patients for out-of-hospital oral treatment.[43]

3.3 Maintenance of Sinus Rhythm After Cardioversion

Safety considerations should guide the choice of antiarrhythmic drug therapy once SR has been restored.[12] In two placebo-controlled trials,[44,45] comparative studies with quinidine[46,47] and in uncontrolled studies,[48,49] flecainide was effective for maintaining SR after cardioversion of AF reducing the number of AF recurrences and lengthening the time between episodes. Flecainide use approximately doubled the likelihood of maintaining SR.[12]

In comparative studies, flecainide efficacy was comparable with that of quinidine with fewer side effects.[46,47] In uncontrolled studies, severe ventricular proarrhythmia or sudden death was not observed at a mean dose of 199 mg daily among patients with little or no structural heart disease. Adverse effects (9%) were predominantly related to negative dromotropism with or without syncope. Flecainide (200 mg daily) was superior to long-acting quinidine (1100 mg daily) in preventing recurrent AF after cardioversion and was associated with fewer side effects, although one patient died a month after entry, presumably due to proarrhythmia.[49]

A meta-analysis of 60 studies with oral and/or intravenous flecainide showed that 65% of patients were responsive to treatment in the short term and 49% in the long term, indicating that the clinical benefit of flecainide for maintaining SR is sustained.[50] Flecainide is more effective than other antiarrhythmic drugs, including propafenone, quinidine, disopyramide and sotalol for maintaining SR following cardioversion.[32,33] In addition, flecainide reduces the symptoms associated with AF. In one study, significantly more patients receiving treatment with flecainide reported suppression of palpitations ($p < 0.001$), tachycardia ($p = 0.027$), dyspnoea ($p = 0.003$), and chest pain ($p = 0.023$) compared with those receiving placebo.[44] One in three patients (31%) in the flecainide group reported complete freedom from symptoms, compared with only 9% in the placebo group. Another 24-week study evaluated the efficacy of controlled-release flecainide (200 mg) for the long-term prevention of paroxysmal AF (PAF) in 227 outpatients.[10] The estimated treatment success rate was 74% and the incidence of PAF episodes, whether symptomatic or not, documented from Holter recording decreased from 28.6% at baseline to 11.0% ($p < 0.0001$).

4. Safety Data

The first data indicating that flecainide should be avoided in patients with underlying heart disease came from the CAST trial.[6,7] CAST enrolled post-myocardial infarction (MI) patients with asymptomatic or mildly symptomatic ventricular arrhythmias (≥6 PVCs per hour). Despite showing effective suppression of ventricular arrhythmias initially, patients treated with the class Ic agents flecainide and encainide had a higher rate of death from arrhythmia than those assigned to placebo, causing the trial to be terminated early. Specifically, the relative risk (RR) of non-fatal cardiac arrest and death from arrhythmia was 3.6 (95% CI 1.7, 8.5) for recipients of flecainide or encainide compared with placebo. In addition, total mortality was higher in the flecainide/encainide group versus placebo (RR 2.5; 95% CI 1.6, 4.5). The applicability of the CAST results to other populations is uncertain, but it is prudent to consider the risks of flecainide generally unacceptable in patients without life-threatening ventricular arrhythmias. However, when used in patients with supraventricular arrhythmias without structural heart disease, and when drug plasma levels are maintained within the therapeutic range (0.2–1 μg/mL), flecainide has been shown to have a good safety profile.[8,51]

4.1 Cardiac Adverse Events

4.1.1 Proarrhythmia

Provocation or exacerbation of an arrhythmia that is different or more severe than the baseline arrhythmia during treatment with antiarrhythmic drugs is called proarrhythmia.[52] Proarrhythmic effects occur with all antiarrhythmic drugs, including a variety of agents used for the cardioversion or prevention of recurrences of AF (table II).[53] Furthermore, all drugs that prolong action potential duration have the potential to cause torsades de pointes.[54] The theoretical risk of torsades de pointes with flecainide is low because it does not affect ventricular repolarization and, therefore, does not alter the JT interval.[55]

Class Ic antiarrhythmic agents appear most likely to have ventricular proarrhythmic effects in patients with wide QRS duration (>120 ms), structural heart disease, LV dysfunction, ventricular scar tissue or coexisting ventricular arrhythmias.[56,57] This is the phenomenon believed to be responsible for the adverse outcome observed in flecainide and encainide recipients in CAST.[6,7]

Table II. Proarrhythmic effects of class I antiarrhythmic agents used to convert AF to sinus rhythm (reproduced from Boriani et al.,[53] with permission from Adis, a Wolters Kluwer business. © Adis Data Information BV 2004. All rights reserved)

Antiarrhythmic	Proarrhythmic effects	Frequency
Potentially all agents	VT or VF	Rare, except in the presence of CAD, LV dysfunction or HF
All class Ia agents	Transformation of AF to atrial flutter with higher VR	Rare
	Torsade de pointes	1–8%
All class Ia and Ic agents	High-grade AV block	Rare
Flecainide Propafenone	Transformation of AF to atrial flutter with 1 : 1 AV conduction and wide QRS	3.5–5%

AF = atrial fibrillation; **AV** = atrioventricular; **CAD** = coronary artery disease; **HF** = heart failure; **LV** = left ventricular; **VF** = ventricular fibrillation; **VR** = ventricular rate; **VT** = ventricular tachycardia.

Ventricular proarrhythmic effects seem to be rare when there is preserved LV function and in the absence of other predisposing factors such as electrolyte disturbances.[53] In a recent systematic review, the incidence of ventricular arrhythmias was less than 3% in patients treated with flecainide for acute conversion of AF.[33] Another meta-analysis of 122 prospective studies was conducted in 4811 patients (mean age 55 ± 13 years, 60% male) with supraventricular arrhythmias and no significant signs of LV damage.[8] The total exposure time was 2015 patient years, with a mean oral flecainide dose of 216 ± 65 mg/day. The rate of proarrhythmic events was significantly lower in flecainide compared with placebo recipients (2.7% vs 4.8%; $p < 0.001$). There was also no significant difference between the flecainide and control groups in the rate of sudden cardiac death or total mortality, and the incidence of syncope (0.1% vs 0.2%) and hypotension (0.8% vs 1.3%) was significantly less frequent with flecainide. There were 120 proarrhythmic episodes observed in 120 flecainide-treated patients and 88 in control patients ($p < 0.001$). This meta-analysis also revealed that flecainide was associated with less diarrhoea (0.7% vs 2.8%), headache (2.0% vs 2.9%) and nausea (1.6% vs 1.8%) than controls, and that less than 5% of patients receiving flecainide discontinued treatment due to adverse effects.[8] These data clearly show that the use of flecainide in patients with supraventricular arrhythmias is safe and, because of its proven efficacy, advisable.

In the study by Aliot et al. investigating the effect of controlled-release flecainide in 227 patients with PAF (previously discussed in section 3.3), the mean maximum QRS increase from baseline was 11.4% and only four patients had a maximum QRS value >100 ms under treatment.[10] QRS was <15% in 71.8% of patients and ≥25% in 18.8% of patients. Bradycardia (13.2%; n = 17/129) and ventricular extrasystoles (10.6%; n = 11/104) were the most frequently identified proarrhythmic effects. AV block (4.0%; n = 9/227), supraventricular tachycardia (2.2%; n = 4/227) and bundle branch block (1.8%; n = 4/227) were the most frequent drug-related cardiac adverse events. Cardiac adverse events resulted in treatment discontinuations in 6.6% of patients, including 2.2% who discontinued due to a proarrhythmic effect. Other evidence has shown that new or worsened arrhythmias occurred in 1% of 108 patients with PSVT and in 0.4% (2/568) of patients with parosysmal atrial fibrillation/flutter treated with oral flecainide.[28] However, in patients with chronic AF, 10.5% developed ventricular tachyarrhythmias; therefore, flecainide is not recommended in these patients. New or exacerbated ventricular arrhythmias occurred in 7% of 1330 patients with PVCs, non-sustained or sustained VT. Among patients treated for sustained VT (who frequently also had congestive heart failure [CHF], a low ejection fraction or a history of MI), the incidence of proarrhythmic events was 13% when dosage was initiated at 200 mg/day with slow upward titration, and did not exceed 300 mg/day in most patients. When using a higher starting dose (400 mg/day) the incidence of proarrhythmic events was 26%. Because of the high frequency of proarrhythmic events flecainide is contraindicated in patients with sustained VT and

underlying heart disease, and drug therapy should be started in hospital following the recommended dosage schedule.

4.1.2 Conduction Abnormalities

Flecainide dose-dependently slows intracardiac conduction, with the greatest effect on the His-Purkinje system (H-V conduction), and prolongs the PR (17–29%), QT (4–11%) and QRS (11–27%) intervals.[2,3,13,58-61] Most of the QT prolongation is due to a widening of the QRS complex[2,59] so that the JT interval and the rate-corrected QT interval (QTc) remains unchanged or slightly increased (3–8%).[2,3,13,15,59-62] Flecainide also prolongs atrial, AV nodal and ventricular refractoriness, but the effects on refractoriness are less pronounced than its effects on intracardiac conduction.[2,3,13,15,58-61,63] If second- or third-degree AV block, or right bundle branch block associated with a left hemiblock occurs, flecainide should be discontinued unless a ventricular pacemaker is in place.

Flecainide can organize and slow the rate of AF, converting it to atrial flutter, which in some patients with a particularly slow atrial rate may result in 1 : 1 AV conduction with a rapid ventricular response. The reported incidence of this complication is 3.5–5% (table II).[53,64] This complication is a risk that has limited the prescription of flecainide in patients with supraventricular arrhythmias,[9] and is more likely to occur in the presence of adrenergic stimulation. AV nodal blocking drug (like β-blockers, verapamil, diltiazem and digoxin) may lower the risk of this complication.[53]

4.1.3 Haemodynamic Effects

Flecainide does not modify heart rate, although bradycardia and tachycardia have been reported,[2,3] but increases the corrected sinus node recovery time and the SA conduction time in patients with sinus node dysfunction.[3,62,65] Intravenous flecainide transiently reduces cardiac output and stroke volume.[66]

Multiple doses of oral flecainide had minimal effects on LV ejection fraction in patients with nearly normal ventricular function.[3] However, flecainide exerts a negative inotropic effect and may cause or worsen heart failure in patients with coronary heart disease, pre-existing heart failure (New York Heart Association functional class III–IV) or LV dysfunction (LV ejection fraction <30%).[67-72] New or worsened CHF developed in 0.4% (1/225) of patients with supraventricular arrhythmias,[28] and in 6.3% of 1046 patients with PVCs, non-sustained or sustained VT.[28] In patients with a history of CHF, 25.7% (78/304) developed worsened CHF.[28] Therefore, flecainide use is contraindicated in patients with a history of congestive HF or LV dysfunction.

4.2 Non-Cardiac Adverse Events

Almost all non-cardiac adverse events that occur during flecainide therapy are mild, transient and tolerable. Furthermore, inability to tolerate flecainide usually becomes evident early in the course of treatment.[73] The most common non-cardiac adverse events associated with flecainide in a clinical trial in patients with ventricular arrhythmia are described in table III. CNS-related side effects during flecainide therapy are not unexpected given that the drug has some local anaesthetic properties.[73] Dizziness, the most frequent non-cardiac event, is the most common cause of discontinuation of therapy. Flecainide also produces adverse visual effects, which are generally transient and mild or moderate in severity.[73] Events occurring in fewer than 3% of flecainide recipients include ataxia, flushing, increased sweating, twitching and vertigo. Peripheral neuropathy is rare but may be clinically significant and can occur following prolonged flecainide use.[74] Very few psychiatric adverse experiences have been reported, but there are a few reports of severe toxicity.[75-77] In a meta-analysis of 122 prospective studies conducted in patients with supraventricular arrhythmias and no significant signs of LV damage, the rates of dizziness ($p = 0.06$), visual disturbances ($p < 0.001$) and other CNS effects ($p < 0.001$) were higher with flecainide versus controls, but gastrointestinal disturbances were significantly more frequent in the control group ($p < 0.001$).[8] In acute and chronic administration studies of the drug, other adverse effects described in 1–3% of patients included a wide range of cardiovascular, gastrointestinal,

Table III. Most common non-cardiac adverse events in patients with ventricular arrhythmia in a multicentre study[28]

Adverse event	Incidence in all patients at any dose (%) [n = 429]	Incidence by dose during up-titration (%)		
		200 mg/day [n = 426]	300 mg/day [n = 293]	400 mg/day [n = 100]
Dizziness[a]	18.9	11.0	10.6	13.0
Visual disturbances[b]	15.9	5.4	12.3	18.0
Dyspnoea	10.3	5.2	7.5	4.0
Headache	9.6	4.5	6.1	9.0
Nausea	8.9	4.9	4.8	6.0
Fatigue	7.7	4.5	4.4	3.0
Asthenia	4.9	2.6	2.0	4.0
Tremor	4.7	2.4	3.4	2.0
Constipation	4.4	2.8	2.1	1.0
Oedema	3.5	1.9	1.4	2.0
Abdominal pain	3.3	1.9	2.4	1.0

a Included reports of dizziness, light-headedness, faintness, unsteadiness, near syncope, etc.

b Included reports of blurred vision, difficulty in focusing, spots before eyes, etc.

cutaneous, visual, nervous system and psychiatric events.[28] There have also been rare reports of isolated elevations of serum transaminase levels and hepatic dysfunction, including cholestasis and hepatic failure, and very rare reports of blood dyscrasias. However, no causal relationship has been established.

4.3 Safety Results from More Recent Clinical Trials

The majority of clinical trials with flecainide now exclude patients with heart failure, LV dysfunction, cardiac hypertrophy and/or ischaemic heart disease, in line with current treatment guidelines. A number of clinical trials have reported a good tolerability profile for flecainide in groups of appropriately selected patients.

4.3.1 Acute Cardioversion

Intravenous administration of flecainide 2 mg/kg over 20 minutes (maximum 200 mg) converted recent-onset AF to SR in 56% of patients and the incidence of adverse effects was 12%.[78] Events included chest pain (n = 2), dizziness (1), hypotension (3), acute congestive heart failure (1), atrial flutter with 1 : 1 AV conduction (1), bradycardia (2) and bifascicular block (2). In this trial, the tolerability of flecainide was similar to that of ibutilide (1 or 2 doses of 1 mg given intravenously over 10 minutes).

The authors of a study assessing the efficacy and tolerability of an out-of-hospital, self-administered, single oral dose of flecainide in patients with PSVT considered that "minor drug-related adverse effects were accepted by patients in comparison with the associated clinical benefit."[79] Adverse events in flecainide recipients were hypotension after drug administration necessitating electrical cardioversion (n = 2) and sinus bradycardia (n = 1). Five patients experienced minor non-cardiac effects during flecainide therapy (nausea, cephalea and sweating). A literature review of seven trials using a single oral loading dose of flecainide for pharmacological conversion of recent-onset AF documented reversible QRS widening, arrhythmias and LV decompensation as the cardiac side effects of therapy.[35] Mild non-cardiac events also occurred. All adverse events were transient. There were no serious non-cardiac events, ventricular arrhythmias or deaths during flecainide therapy.[35]

Many patients with AF have coexisting heart disease. Although long-term prophylactic use of class Ic antiarrhythmics may not be appropriate in terms of proarrhythmic risk,[6,7] there are comparatively little data on the use of a single dose of flecainide in patients with structural heart disease. A recently published prospective observational study recruited 106 patients with new-onset AF who had additional cardiac risk factors (one or

more of the following: coronary heart disease, dilated cardiomyopathy with reduced LV ejection fraction, heart failure, PROCAM score >41) and treated them with a single oral dose of flecainide 300 mg.[80] No cases of life-threatening ventricular arrhythmias, or intervention for AV conduction abnormalities or atrial flutter were documented during the study. Thirty-six of the 43 patients with successful flecainide-induced cardioversion developed asymptomatic sinus bradycardia.[32] However, prospective studies are not permitted in this patient population due to ethical concerns around patient safety.[12]

4.3.2 Prophylactic Use

When used to prevent the recurrence of PAF, flecainide has been shown to have a good safety profile.[10,51,81] In one clinical trial, the adverse event rate monitored with transtelephonic ECG was similar in patients receiving placebo or flecainide 50, 100 or 200 mg/day.[81] The most common non-cardiac side effect was headache, but there was no evidence of ventricular proarrhythmia and no deaths occurred during the study. Five flecainide recipients required hospitalization and/or cardioversion or ablation, and one patient receiving the highest dosage had a sinus arrest.[81]

In another trial using controlled-release flecainide to prevent PAF in 227 outpatients (previously discussed in section 4.1.1), almost 7% and 5% of patients discontinued therapy due to cardiac and non-cardiac adverse events, respectively.[10] The study authors suggested that their data provide "evidence for a good cardiac safety profile of the 200 mg controlled-release formulation of flecainide."[10]

4.4 Special Populations

4.4.1 Patients with Renal Dysfunction

Flecainide is excreted mostly in urine and accumulates in patients with renal failure.[66] The absorption and volume of distribution of flecainide are not altered in patients with renal dysfunction, but the elimination half-life is prolonged, increasing in parallel with the severity of renal impairment, from 11.5 hours in patients with normal renal function (mean glomerular filtration rate [GFR] >90 mL/min/1.73 m^2) to 19.9 hours in those with impaired renal function (mean GFR 37.8 mL/min/1.72 m^2).[82] The time to reach peak plasma levels may also take longer than 4 days. End-stage renal disease (GFR <15 mL/min/1.73 m^2 or dialysis) may prolong the half-life to 51–58 hours.[66,83] Thus, lower starting and maintenance dosages and frequent monitoring of plasma levels and ECG parameters may be necessary in patients with moderate-to-severe renal dysfunction (GFR 15–59 mL/min/1.73 m^2).[48] Monitoring is particularly relevant in patients undergoing dialysis because flecainide is poorly dialysed.[9]

4.4.2 Patients with Hepatic Dysfunction

Because flecainide is extensively metabolized its elimination rate can be markedly slower in patients with significant hepatic impairment. Thus, flecainide should not be used in these patients unless the potential benefits clearly outweigh the risks and if used, frequent plasma level monitoring is required.

4.5 Warnings and Precautions

Patients with electrolyte disturbances, especially hyperkalaemia or hypokalaemia, should have these corrected prior to the initiation of flecainide to avoid any alteration in drug effects.[28] In addition, physicians should be aware that flecainide increases endocardial pacing thresholds. While this effect is reversible, flecainide should be used with caution in all patients with permanent pacemakers or temporary pacing electrodes and not used at all in those who already have poor thresholds or non-programmable pacemakers unless appropriate pacing rescue is available.[28] Caution is also recommended if flecainide is used in patients with acute onset of AF after cardiac surgery,[84] and is not recommended in those with a history of congestive heart failure or LV dysfunction.[12,28]

4.5.1 Mortality

Flecainide increases the rate of death and non-fatal cardiac arrest in post-MI patients with asymptomatic PVCs and non-sustained VT compared with placebo (5.1% vs 2.3%).[6] There is no evidence of improved survival or reduced incidence of sudden cardiac death, and there is evidence of harm in a subgroup of patients (those with asymp-

tomatic non-life-threatening ventricular arrhythmias with previous MI).[6] Therefore, use of class Ic agents for ventricular tachyarrhythmia, including flecainide, is not recommended in patients without life-threatening arrhythmias.[28]

According to registry data, use of antiarrhythmics did not increase the risk of death in Danish patients treated between 1995 and 2004.[85] Of the 141 500 patients analysed, 3356 were treated with flecainide at a mean dosage of 205.6 mg. The mortality rate was 2.54 per 100 person years and this compares favourably with the corresponding rates for patients treated with propafenone (4.25), sotalol (5.29) and amiodarone (7.42). It also indicates that patients are being appropriately selected for antiarrhythmic drug therapy.[85]

4.6 Contraindications

Flecainide is contraindicated in patients with pre-existing second- or third-degree AV block, or right bundle branch block when associated with a left hemiblock, unless a pacemaker is present to ensure an adequate ventricular rate, and in the presence of cardiogenic shock, cardiac failure, previous MI, haemodynamically significant valvular heart disease, long-standing untreated AF or known hypersensitivity to the drug.[28,62,84] It should be used only with extreme caution in patients with sick sinus syndrome because it may cause sinus bradycardia, sinus pause, or sinus arrest.

4.7 Overdose

Drug overdose with flecainide is frequently fatal. Mortality has been reported to be as high as 10% with flecainide overdose compared with less than 1% for all drug overdoses,[86] although patients have survived after taking flecainide doses of up to 8000 mg and reaching peak plasma levels of 5.3 μg/mL. These patients presented with a range of symptoms including CNS effects (dizziness, tremor, ataxia, seizures), pulmonary oedema, slowed breathing, blurred vision, photophobia, hypotension, bradycardia, syncope, marked widening of the QRS complex and PR and QT intervals, ventricular tachyarrhythmias, AV nodal block, asystole, bundle branch block, cardiac failure, electro-mechanical dissociation and cardiac arrest.[28,86,87]

Very recently, a retrospective, observational cohort study enrolling 112 patients with paroxysmal (51%) or persistent (49%) AF found that flecainide treatment (mean dose 203 mg/day) was associated with an increased risk of cardiovascular mortality (related to sudden cardiac death or proarrhythmic events) compared with the general Swedish population.[11] These findings suggest that further investigation into the safety of flecainide in AF patients is warranted. However, this is a retrospective study in which all information was collected retrospectively from medical records and 50% of the patients were in persistent AF where flecainide is not indicated.[12]

There is no specific antidote for the treatment of flecainide overdose. All patients with potential drug-related toxicities should discontinue flecainide. Treatment of overdose should be supportive, including removal of unabsorbed drug from the gastrointestinal tract (gastric lavage, activated charcoal), volume expansion, hypertonic sodium bicarbonate (in the treatment of widened QRS and ventricular ectopy), inotropic support (with dopamine, dobutamine or isoproterenol), and mechanically assisted respiration. Cardiopulmonary bypass support may be necessary in order to temporarily obviate the need for a beating heart, and insertion of a pacemaker in the presence of bradycardia, AV block or ventricular dysrrhythmias may also be required. Hypertonic sodium bicarbonate competes with the binding of flecainide to the Na^+ channels, reversing the effect of flecainide on cardiac excitability and conduction.[88,89] Ventricular arrhythmias may be difficult to cardiovert electrically and both lidocaine and amiodarone have been used successfully in such cases.[88,90,91] Because of the long plasma half-life of flecainide and the non-linear elimination kinetics at very high doses, these treatments need to be continued for extended periods of time.

5. Drug Interactions

Known drug interactions with flecainide (both pharmacokinetic and pharmacodynamic) are briefly described in this section.

5.1 Amiodarone

Amiodarone inhibits CYP2D6.[92,93] Co-administration of amiodarone decreases hepatic metabolism and renal clearance of flecainide, increasing flecainide plasma concentrations by 2-fold or more.[92,93] It is recommended that the flecainide dose be halved when given in combination with amiodarone and to monitor flecainide plasma levels.[92,93] Due to the long half-life of amiodarone (28–130 days) this interaction can also be observed when initiating flecainide therapy in patients who have recently been treated with amiodarone.

5.2 β-Blockers (Class II Antiarrhythmics)

The co-administration of flecainide and propranolol increased the plasma levels of both drugs by 25% compared with control values, which may exert an additive negative inotropic effect and prolong the PR interval.[28,84,94]

5.3 Cimetidine

In healthy volunteers, co-administration of cimetidine and flecainide decreased renal clearance and increased the half-life and plasma levels (30%) of the latter drug. However, information on this interaction is limited and its clinical relevance is not known.[17]

5.4 Digoxin

Digoxin concentrations increase by 15–19% 6 hours after co-administration with flecainide.[94-96] Therefore, close monitoring of serum digoxin concentrations is recommended during combination therapy.[94-97]

5.5 Diuretics

Co-administration of diuretic agents may exacerbate electrolyte loss when given with flecainide, leading to hyponatraemia-induced flecainide cardiotoxicity.[98]

5.6 Selective Serotonin Reuptake Inhibitors

Plasma concentrations of flecainide may be increased by concomitant administration of selective serotonin reuptake inhibitors. Dose reduction has not been clinically assessed but may be warranted to avoid potential proarrhythmic effects during combination therapy.[99] Gene polymorphisms may play a role, with the extent of drug interaction between flecainide and paroxetine being shown to be influenced by the CYP2D6*10 allele.[100]

5.7 QTc-Prolonging Agents

Combination of flecainide with QTc-prolonging drugs (e.g. artemether, dronederone, lumefantrine, nilotinib, pimozide, quinine, tetrabenazine, thioridazine, ziprasidone) should be avoided because co-administration of two agents that prolong the QTc interval is not advised (table IV).[28]

5.8 Urinary Alkalinizers

Renal excretion of flecainide is a pH-dependent process. In healthy volunteers, drugs that alkalinize the urine decreased urinary excretion of flecainide and increased its elimination half-life.[24,102] However, wide inter-individual variability was observed

Table IV. Recommendations for flecainide therapy during co-administration of other agents with drug interaction potential[84,101]

Monitor therapy	Consider therapy modification	Avoid combination
Alfuzosin	Amiodarone	Artemether
Carbonic anhydrase inhibitors	Bupropion	Dronedarone
Chloroquine	Gadobutrol	Indinavir
Ciprofloxacin	QTc-prolonging agents	Lopinavir
CYP2D6 inhibitors (moderate)	CYP2D6 inhibitors (strong)	Lumefantrine
Darunavir		Mizolastine
Etravirine		Pimozide
PEG interferon-α2b		Quinine
Sodium bicarbonate		Ritonavir
Sodium lactate		Terfenadine
Tromethamine		Tetrabenazine
Verapamil		Thioridazine
		Tipranavir
		Ziprasidone

CYP = cytochrome P450; **PEG** = pegylated; **QTc** = corrected QT interval.

and the clinical significance of these findings remains to be determined.

5.9 Other Agents

Flecainide therapy should also be monitored during coadministration of carbonic anhydrase inhibitors except brinzolamide and dorzolamide (these agents may decrease excretion of flecainide); sodium lactate and tromethamine (serum concentration of flecainide may be increased); etravirine and pegylated-interferon-α2b (potential decrease in serum concentration of flecainide); sodium bicarbonate (may decrease the efficacy of flecainide); and disopyramide and verapamil (combination may impair myocardial contractility and AV nodal conduction) [table IV].[101]

Concurrent use with CYP2D6 inhibitors may increase plasma flecainide levels, especially in extensive metabolizers, hence the dose of flecainide should be reduced accordingly (table IV). Conversely, inducers of CYP2D6 (e.g. phenytoin, phenobarbital, carbamazepine) may modestly increase flecainide clearance. Tobacco stimulates cytochrome P450 in the liver and increases the clearance of flecainide, so that smokers need larger doses of flecainide to achieve the same therapeutic effects.[103]

6. Use During Pregnancy and Lactation

Flecainide is classified as Pregnancy Category C, which means that animal reproduction studies have shown an adverse effect on the foetus. However, there are no adequate and well controlled studies in humans, and the potential benefits may warrant use of the drug in pregnant women despite potential risks for the foetus. However, flecainide has been used safely during human pregnancy to treat foetal tachycardia.[104,105] The influence of flecainide use during labour and delivery is currently unknown.[28] Excretion of flecainide into human breast milk has been documented at drug concentrations an average of 2.5 times higher than corresponding maternal plasma levels.[106] However, the expected average steady-state plasma concentration of flecainide in a newborn infant consuming 700 mL/day of breast milk would be expected to be low, ≤62 ng/mL, suggesting that the risk is very small.[106] Thus, flecainide is considered compatible with breast-feeding by the American Academy of Pediatrics.

7. Paediatric Use

The safety and efficacy of flecainide has not been studied in paediatric patients in double-blind, randomized, placebo-controlled trials. In children with structural heart disease, flecainide has been associated with cardiac arrest and sudden death and therefore, it should be directly supervised by a paediatric cardiologist.

8. Conclusions

Flecainide is a drug of choice for the management of patients with paroxysmal AF because it is effective, has a good safety record and low incidence of adverse effects, rare end-organ toxicity, and a low risk of ventricular proarrhythmia.[107] Thus, flecainide has a role in the management of patients with AF in carefully selected groups of patients according to the ESC guidelines.[12] To ensure the benefits of treatment outweigh the risks, careful patient monitoring is required and the patient's condition must be taken into account and regularly re-evaluated.[12] In addition, flecainide's therapeutic value and dosage should be routinely reassessed.

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