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Review

Current strategies of antiarrhythmic drug therapy for paroxysmal atrial fibrillation

Takashi Komatsu, MD*

Division of Cardioangiology, Nephrology and Endocrinology, Department of Internal Medicine, Iwate Medical University, 19-1, Uchimaru, Morioka 020-8505, Japan

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ABSTRACT

Atrial fibrillation is now recognized as a significant medical and social problem. Atrial fibrillation not only causes cardiovascular complications, including thromboembolism and heart failure, but also decreases the survival of patients with impaired left ventricular function; thus, it is considered an independent factor for cardiovascular death. The goal of antiarrhythmic drug therapy for atrial fibrillation is improvement of daily quality of life and cardiovascular prognosis in maintaining sinus rhythm, while ensuring the safety of antiarrhythmic drugs. Antiarrhythmic drugs are prescribed to prevent recurrence of atrial fibrillation; however, they demonstrate limited efficacy. Recently, catheter ablation has been established as a promising new therapy to prevent recurrence of atrial fibrillation, even though this procedure would be difficult to apply clinically because of its complications and the large number of patients requiring treatment. Since the antiarrhythmic drugs remain the first-line, primary therapy for paroxysmal atrial fibrillation, clinicians should select appropriate antiarrhythmic drugs for treatment of paroxysmal atrial fibrillation based on individual patient characteristics.

Herein, I review the current strategies of antiarrhythmic drug therapy for paroxysmal atrial fibrillation from the point of view of pharmacological prevention of atrial fibrillation recurrence, improvement of patient quality of life, and cardiovascular prognosis.

Contents

1. Approach to antiarrhythmic drug therapy

1.1. Indications for rhythm control therapy

Various factors are involved in the development of atrial fibrillation (AF), including the condition of the autonomic nervous system, underlying heart disease, hemodynamic disorders, inflammation, endocrine disorders, electrolyte imbalance, oxidative stress, and concomitant drug use. The specific factors that affect the development of AF and the extent of their effects differ among patients. It is important to investigate the possible causes of AF, which manifests across a wide variety of clinical profiles, in order to understand the pathophysiology of this condition and to determine treatment strategies for individual patients.

Generally, rhythm control therapy using antiarrhythmic drugs is positively indicated for (1) patients with severe subjective symptoms negatively affecting quality of life (QOL); (2) patients with paroxysmal AF; (3) patients with without or with mild

* Tel.: +81 19 651 5111x2324; fax: +81 19 651 0401.
E-mail address: sym.koma@imu.ncvc.go.jp

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underlying heart disease; (4) patients without or with slight (< 50 mm) increase in left atrial dimension; and (5) patients in whom AF causes an abrupt disturbance of hemodynamics or acute worsening of myocardial ischemia. On the other hand, rate control therapy is indicated for (1) asymptomatic patients and those with subjective symptoms having little or no effect on QOL; (2) patients with permanent AF; and (3) patients with a significant increase in left atrial dimension (≥ 50 mm).

1.2. Examinations required prior to rhythm control therapy

Patients should undergo chest X-ray, standard 12-lead electrocardiogram (ECG), blood examination, transthoracic echocardiography, ambulatory 24-h ECG monitoring, exercise ECG, brain computed tomographic (CT) examination or magnetic resonance imaging (MRI), and other appropriate tests prior to the initiation of treatment. Table 1 summarizes the key points to be examined in these tests. Patients with hepatic and/or renal dysfunction should be treated with drugs that do not negatively affect the metabolic pathways of antiarrhythmic drugs. Patients with electrolyte imbalances such as hypokalemia and hypocalcemia are prone to proarrhythmic adverse effects from antiarrhythmic drugs. Since the metabolism and excretion of antiarrhythmic drugs are slow and blood concentrations of these drugs tend to increase in elderly patients, physicians must carefully select and modify the maintenance doses of antiarrhythmic drugs and the type of drugs used concomitantly. Table 2 lists the antiarrhythmic drugs currently available in Japan, their pharmacokinetics, their effective blood concentrations, and excretion mechanism.

Table 1
Examinations required prior to rhythm control therapy.

I. Chest radiography
Cardiomegaly, pulmonary congestion, hydrothorax, underlying heart diseaseunderlying pulmonary disease, etc.
II. Standard 12-lead electrocardiography
Heart rate, PQ interval, QRS duration QT interval, ST-T change, etc.
III. Blood examination
Renal and liver function, electrolyte, serum concentration of antiarrhythmic drug, atrial naturiuretic peptide, brain naturiuretic peptide, D-dimer, prothrombin time- international normalized ratio, etc.
IV. Transthoracic or transesophageal echocardiography
Underlying heart disease, cardiac function, enlarged right or left atrium, intracardiac thrombus, spontaneous echo contrast, velocity of left appendage or pulmonary vein, aortic atheroma, etc.
V. Ambulatory 24-hr monitoring
Phramacological evaluation, rate control, sick sinus syndrome or asymptomatic atrial fibrillation, etc.
VI. Treadmill or ergometer exercise test
Myocardial ischemia, provocation of arrhythmia, rate control, etc.
VII. Computed tomographic examination / magnetic resonance image Ischemic or hemorrhagic stroke, etc.

2. Preventive efficacy of antiarrhythmic drugs

2.1. Efficacy in maintaining sinus rhythm in patients with paroxysmal AF (patients with episodes of AF that terminate spontaneously within 7 day)

2.1.1. Results of studies in Western countries

In Western countries, the percentage of patients who maintained sinus rhythm after treatment with the Class I antiarrhythmic agent flecainide (100–300 mg/day) was 61–71% after 6 months of treatment [1–3] and 62–77% after 12 months [3–5]. The corresponding percentage in patients receiving the Class I agent propafenone (450–1,200 mg/day), was 57% after 6 months [6] and 45–55% after 12 months [4–8]. For Class III drugs, the corresponding percentages were 46–50% [9,10] and 37–70% [8,10] after 6 and 12 months of treatment with sotalol, respectively (160–690 mg/day), and 50–80%[11–13] after 12 months of treatment with amiodarone (200–300 mg/day).

Recently, the Canadian Trial of Atrial Fibrillation (CTAF), a large randomized study comparing the efficacy of Class I and III drugs in preventing recurrent AF [14], reported that the percentage of patients with no AF recurrence after 12 and 24 months of treatment were 66% and 51%, respectively, in those treated with amiodarone (mean dosage: 186 ± 48 mg/day). These percentages were higher than those of propafenone (45% and 37%, respectively; mean dosage 471 ± 121 mg/day) and sotalol (48% and 34%, respectively; mean dosage 224 ± 83 mg/day; Fig. 1). In a subanalysis of the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) study, the percentage of patients without recurrence of AF at a 12-month follow-up were 62%, 38%, and 23% for those treated with amiodarone, sotalol, and Class I drugs, respectively, demonstrating that amiodarone was the most effective drug for preventing AF recurrence [15]. Regarding dronedarone (400 mg/day), a new agent recently approved in Western countries, it has been reported that the percentages of patients with paroxysmal AF or persistent AF who maintained sinus rhythm after 6 and 12 months of treatment were 50–64% and 35–40%, respectively (Fig. 2) [16,17]. However, a meta-

Table 2
Pharmacokinetics, effective blood concentrations, and excretion mechanism of antiarrhythmic drugs used for treatment of atrial fibrillation. (The description order of antiarrhythmic drugs follow that of Sugi K, Noro M, Sakata T, et al. Pharmacological treatment for atrial fibrillation. J Arrhythmia 2005; 21: 358–370.)

Antiaarhythmic drugs	Cmax (h)	$T_{1/2}$ (h)	Therapeutic levels (μg/ml)	Excretion (%)
Qunidine	1–4	6–8	2–5	Liver(80) · Kidney(20)
Procaineamide	0.5–1.0	3–5	4–12	Liver(40) · Kidney(60)
Disopyramide	2	4–8	2–5	Liver(40) · Kidney(60)
Cibenzoline	1.5	5–6	0.3–1.0	Liver(20) · Kidney(80)
Pirmenol	1.0–1.5	8–10	0.4–1.0	Liver(30) · Kidney(70)
Lidocaine	–	13 min	1–5	Liver(90) · Kidney(10)
Mexiletine	2–4	8–16	0.75–2.0	Liver(90) · Kidney(10)
Aprindine	2–4	9–27	0.25–1.25	Liver (100)
Flecainide	2–4	12–27	0.2–1.0	Liver(15) · Kideny(85)
Propafenone	2–3	2–10	0.2–1.0	Liver(90) · Kidney(10)
Pilsicainide	1–2	4–5	0.2–1.0	Kidney(100)
Amiodarone	3–7	26–107 days	1.0–2.0	Liver (100)
Sotalol	2–4	7–11	1–3.2	Kideny (100)
Verapamil	2	3–7	0.03–0.4	Liver(90) · Kidney(10)
Bepridil	3.1	80	Unknown	Kidney (100)
Adenosine triphosphate	2–3 s	10 s	Unknown	–