CASE STUDIES

ST segment elevation in the right precordial leads following administration of class Ic antiarrhythmic drugs

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Abstract

Electrocardiographic changes were evaluated retrospectively in five patients without previous episodes of syncope or ventricular fibrillation who developed abnormal ST segment elevation mimicking the Brugada syndrome in leads V1–V3 after the administration of class Ic antiarrhythmic drugs. Pilsicainide (four patients) or flecainide (one patient) were administered orally for the treatment of symptomatic paroxysmal atrial fibrillation or premature atrial contractions. The QRS duration, QTc, and JT intervals on 12 lead surface ECG before administration of these drugs were all within normal range. After administration of the drugs, coved-type ST segment elevation in the right precordial leads was observed with mild QRS prolongation, but there were no apparent changes in JT intervals. No serious arrhythmias were observed during the follow up periods. Since ST segment elevation with mild QRS prolongation was observed with both pilsicainide and flecainide, strong sodium channel blocking effects in the depolarisation may have been the main factors responsible for the ECG changes. As the relation between ST segment elevation and the incidence of serious arrhythmias has not yet been sufficiently clarified, electrocardiographic changes should be closely monitored whenever class Ic drugs are given.

(Heart 2001;85:e3)

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Accepted 16 August 2000

Keywords: class Ic antiarrhythmic drugs; Brugada syndrome; ST segment elevation

In 1992, Brugada and Brugada¹ reported a study of eight patients with idiopathic ventricular fibrillation who showed ST segment elevation in the right precordial lead (the Brugada syndrome). Recent studies^{2–4} have reported that class I antiarrhythmic drugs such as flecainide, procainamide, and ajmaline could unmask ST segment elevation in patients with “latent” Brugada syndrome. In addition, we reported the first case⁵ of a patient who had no previous syncope or ventricular fibrillation, but who showed electrocardiographic changes mimicking those of the Brugada syndrome after administration of a class Ic antiarrhythmic drug. Similar cases were presented by us^{6,7} and others^{8–10} in ensuing years. In this article we present five such patients and evaluate retrospectively the mechanisms of precordial ST segment elevation on 12 lead surface ECG in these patients.

Patients and method

This study included five patients (four male and one female) without previous syncope or ventricular fibrillation who showed ST segment elevation in the right precordial leads following administration of class Ic drugs (table 1). Four of the patients visited our outpatient clinic because of palpitations which were caused by supraventricular arrhythmias, and the other patient was admitted to our hospital for acute myocardial infarction between 1994 and 1999. Class Ic drugs were prescribed for the control of supraventricular arrhythmias. There was no family history of life threatening ventricular arrhythmias, syncope, or sudden death in any of the patients. Liver function, renal function, and serum potassium, sodium, and magnesium electrolyte concentrations were within normal range in all of the patients.

Table 1 Patient profiles and electrocardiographic changes

Case	Age/sex	Arrhythmia	Underlying disease	EF (%)	Drug	Dose (mg/day)	Duration of treatment (days)	Amplitude of the maximum ST elevation	QRS width (secs)	
									Before	After
1	70/M	PACs	None	68	P	100	28	2.5 mm (V1, V2)	0.09	0.11
2	62/F	Paf	MVR	62	P	150	14	3.9 mm (V2)	0.1	0.12
3	57/M	Paf	AMI, HT	40	P	200	4	5.3 mm (V3)	0.09	0.11
4	57/M	Paf	None	60	F	200	28	3.6 mm (V2)	0.09	0.1
5	73/M	Paf	SSS, HT	66	P*	150	14	2.7 mm (V1)	0.11	0.12

Paf, paroxysmal atrial fibrillation; PACs, premature atrial contractions; MVR, mitral valve replacement; AMI, acute myocardial infarction; HT, hypertension; SSS, sick sinus syndrome; EF, ejection fraction on echocardiography; P, pilsicainide; F, flecainide; *combined with digoxin.

Figure 1 Case 1. (A) Sinus rhythm with premature atrial contraction (PAC) before drug treatment. (B) Four weeks after initiation of treatment with oral pilsicainide. ECG revealed abnormal ST segment elevation in leads V1–V3. (C) After discontinuation of pilsicainide ST segment elevation returned to normal.

The QRS duration, QTc, and JT interval on ECG were measured and compared before and after administration of class Ic drugs. In addition, the ECG lead with the maximum ST segment elevation and the type of elevated ST segment in its configuration were also evaluated.

Results

Patient profiles and ECG changes are listed in table 1. The QRS duration, QTc, and JT intervals before the administration of the class Ic drugs were within normal range in all the patients. The QRS duration was prolonged in the five patients by 10–22% with an average prolongation of 17%, and the QTc was prolonged by 2–5.1% with an average prolongation of 4.3% (figs 1, 2, and 3). JT intervals

Figure 2 Case 2. (Left strip) Paroxysmal atrial fibrillation (Paf). (Right strip) Two weeks after initiation of oral pilsicainide. ECG revealed atrial flutter with 2:1 atrioventricular conduction with pronounced ST segment elevation at leads V1–V3. Case 3. (Left strip) On the third day of acute anteroseptal myocardial infarction. ECG revealed sinus rhythm with abnormal Q wave and mild ST segment elevation in leads V1–V6 and I, aV_L. Thereafter repeated Paf episodes were noted. (Right strip) Four days after initiation of pilsicainide. ECG exhibited pronounced ST segment elevation in leads V1–V3. After discontinuation of pilsicainide, a combination of oral verapamil and pirlenol effectively prevented the Paf and abnormal ST elevation was not recognised. In this case, left ventricular aneurysm and new ischaemic episodes such as chest pain and elevations in serum myocardial enzymes were not recognised during the ST segment elevation after administration of pilsicainide.

remained unchanged. The ST segment elevation was the coved type in all cases, and the lead with maximum ST segment elevation varied in amplitude from 2.5–5.3 mm. No evidence of coronary artery spasm or other obvious causes for the ST segment elevation were evident. Following discontinuation of the drugs, the ECG changes returned to within normal range. All five patients have since been attending our outpatient clinic every four weeks regularly, and serious arrhythmias or syncope have not been detected so far.

Discussion

The main finding of this study is that abnormal ST segment elevation was presented following administration of class Ic drugs in five patients who experienced no previous syncope or ventricular fibrillation. Although the ST segment elevation was similar to that found in the Brugada syndrome, the relation between the ECG changes and the incidence of serious arrhythmias has not yet been sufficiently clarified. The mechanism of ST segment elevation in conjunction with the relevance of sodium channel blocking effects is discussed.

Class Ic drugs are known to be effective for the treatment of various arrhythmias.¹¹ On the other hand, proarrhythmic effects and other adverse effects^{7–12} have also been reported. Recently, some cases of ST segment elevation in the right precordial leads following administration of class Ic drug were reported by our group^{5–7} and others.^{8–9}

In recent studies, the mechanisms of ST segment elevation in the Brugada syndrome are thought to derive from the transmural heterogeneity in repolarisation across the wall of the right ventricular (RV) outflow tract.^{2–3 12 13} Also, in some patients with the Brugada syndrome, a mutation in the cardiac sodium channel gene SCN5A that could cause the heterogeneity has been described.^{4 14}

In our cases, abnormal ST segment elevation with mild prolongation of the QRS duration and QTc was noted following administration of flecainide and pilsicainide, but there were no changes in the JT intervals. These drugs mainly block sodium channels resulting in a reduction of the amplitude of phase 0 of the action potential. When the amplitude of phase 0 decreases in the subepicardium, phase 1 ends at a more negative potential, and this could bring the membrane potential to a voltage below that required for the activation of the calcium current. As a result of the conduction abnormalities and the reduction of I_{Ca} during the early phase of the action potential, ST segment elevation mimicking the Brugada syndrome could be induced. The appearance of the ST segment elevation only in the right precordial leads in our patients is consistent with the observation that the transient outward current I_{to} is dominant in the right ventricular epicardium. In our cases, both flecainide with a potassium channel blocking effect and pilsicainide without a potassium channel blocking effect induced ST segment elevation. In addition, Nakamura and colleagues⁸ reported that MS-551, a pure potassium channel blocking

Figure 3 Case 4. (Left strip) Paf. (Middle strip) Four weeks after initiation of flecainide. Abnormal ST segment elevation in leads V1–V3 was observed. (Right strip) The ST segment elevation was somewhat improved by tapering down the flecainide to 100 mg daily, and then it returned to normal with the discontinuation of flecainide. In this case, the degree of ST segment elevation seemed to depend on the dose of flecainide. Case 5. (Left strip) Sinus rhythm. (Right strip) Two weeks after initiation of oral pilsicainide for the control of Paf. ECG revealed abnormal ST segment elevation in leads V1–V3. In this case, oral cibenzoline effectively prevented Paf and no ST segment elevation was noted with its administration.

agent with no effect on conduction velocity, did not induce ST segment elevation in a similar patient. Therefore, the mechanism of ST segment elevation with class Ic drugs seemed to be an inhibition of the rapid depolarisation and conduction of the action potential by their strong sodium channel blocking effects. In our cases, ST segment elevation was not induced by the class Ia drugs such as disopyramide, cibenzoline, and pirlmelol. This was considered to be caused by the differences in the strength of the sodium channel blocking effects of class Ia and class Ic drugs.

Although our patients showed ST segment elevation similar to that in the Brugada syndrome, it is not clear whether these patients are at risk for serious arrhythmic events. In a study using body surface mapping, Kasanuki and colleagues¹⁵ demonstrated a conduction delay in the anterior wall and RV outflow tract in some patients with the Brugada syndrome, but only when a secondary R wave was presented in lead V1. Furthermore, Fujiki and colleagues⁹ reported that late potentials on signal averaged ECG were accentuated with ST segment elevation by flecainide. Recently, Brugada and colleagues⁴ demonstrated that class I drugs could identify patients in whom the syndrome is concealed, by unmasking the ECG pattern characteristic of the syndrome with high specificity and sensitivity. Therefore, ST segment elevation with class Ic drugs could be caused by conduction delays and consequent proarrhythmic effects. In our five patients, none had episodes of syncope or ventricular fibrillation, and such ST segment elevation had never been observed after discontinuation of class Ic drugs. However, as they still have the possibility of the concealed form of the Brugada syndrome, careful observation and further evaluation, including genetic analysis (if informed consent could be accepted), will be needed for clarification of the mechanisms of these changes. Moreover, careful observa-

tion should nonetheless be paid to ECG changes during the administration of class Ic drugs.

There were several limitations to this study. First, as this study was performed retrospectively and four of the five patients were followed at our outpatient clinic, more detailed ECG changes such as ambulatory monitoring ECG, signal averaged ECG, or electrophysiologic studies could not be evaluated. Therefore, the mechanisms of ST segment elevation were considered using only the changes of the surface 12 lead ECG. Furthermore, as class Ic drugs were used for relatively short periods and this is only a short term follow up report, the relation between the ST elevation and life threatening arrhythmias was not sufficiently clarified. In addition, more extensive studies to confirm our results will be required since only a small number of patients were studied here.

CONCLUSION

ST segment elevation was observed following administration of class Ic drugs in five patients who had no history of syncope or ventricular fibrillation. The mechanisms of the ECG changes were considered to be mainly caused by the drug's strong sodium channel blocking effects. Although the relation between ST segment elevation and serious arrhythmias has not yet been clarified, ECG changes should always be closely monitored when administering class Ic drugs.

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