Brugada Syndrome Whose ST-segment Changes were Enhanced by Antihistamines and Antiallergenic Drugs

Motoki Matsuki, Nobuyuki Sato, Kanako Matsuda, Masaru Yamaki, Naoki Nakagawa, Naka Sakamoto, Hisanobu Ota, Yasuko Tanabe, Toshiharu Takeuchi, Kazumi Akasaka, Yuichiro Kawamura and Naoyuki Hasebe

Abstract

We describe a case of Brugada syndrome, in which a coved type ST-segment elevation was enhanced by antihistamines and antiallergenic drugs. The patient had been treated with four kinds of antihistamines and antiallergenic drugs. The twelve-lead ECG exhibited a coved type ST-segment elevation in leads V1 and V2, and their enhancement was induced by pilsicainide. After discontinuing those drugs, the ST segment elevation in leads V1 and V2 became reduced. An ICD implantation was selected for the therapy since ventricular fibrillation was induced. Our report discusses the possible contribution of antihistamines and antiallergenic drugs to the Brugada type ST-segment changes.

Key words: Brugada syndrome, antihistamines, antiallergenic drugs


Introduction

There have been numerous reports regarding drug-induced Brugada syndrome. Those drugs have included Na channel blockers, Ca channel blockers, beta blockers, K channel openers, psychotropic drugs, cocaine and alcohol (1). On the other hand, it has been shown that the infusion of dimenhydrinate, a first-generation antihistamine, may cause the Brugada-type ST-segment elevation (2, 3). However, few reports have been published concerning the effects of antihistamines and antiallergenic drugs on the Brugada type electrocardiogram (ECG) changes. We encountered a case of Brugada syndrome, in which the coved type ST-segment elevation was remarkably enhanced by oral antihistamines and antiallergenic drugs. We hereby discuss the possible contribution and mechanisms of the effects of the antihistamines and antiallergenic drugs on the Brugada type ST-segment changes.

Case Report

A 53-year-old man was admitted to the Asahikawa Medical College hospital for close examination of an ECG abnormality. He had a family history of sudden cardiac death. Since he had suffered from severe chronic eczema, he had been treated with four different kinds of antihistamines and antiallergenic drugs; homochlorcyclizine hydrochloride (a first generation histamine H1 antagonist), fexofenadine hydrochloride (a second generation histamine H1 antagonist), epinastine hydrochloride (a second generation histamine H1 antagonist), and d-chlorphenilamine maleate (a first generation histamine H1 antagonist). On admission, his blood count, biochemistry, and electrolytes were within normal limits. The twelve-lead ECG on admission (in the presence of antihistamines) revealed a coved type ST-segment elevation in lead V1 and saddle-back type ST-segment elevation in lead V2 (Fig. 1), and that elevation was enhanced by a 50 mg administration of pilsicainide (Fig. 2). The echocardiographic study and magnetic nuclear imaging were normal. Late potentials before and after the antihistamines were...
Figure 1. An ECG after admission. An ECG recorded from the third intercostal space is also shown.

Figure 2. ECG changes induced by a 50 mg pilscainide administration. Although the coved type ECG pattern in lead V1 was not prominent at that time due to discontinuation of the antihistamines, a remarkable ST-segment elevation in leads V1 and V2 associated with a QRS widening was induced by the pilscainide provocation.

found to be positive on the signal-averaged ECG. In the coronary angiogram, no stenosis was detected. In the electrophysiologic study, ventricular fibrillation was easily induced by catheter manipulation in the right ventricular outflow tract (Fig. 3), and hence, this case was diagnosed as Brugada syndrome. A treadmill exercise test revealed ST-segment depression during exercise and ST-segment elevation associated with T wave alternance after exercise. After discontinuing the antihistamines and antiallergenic drugs, the coved type ST segment elevation in leads V1 and V2 changed to a saddleback type and the depth of the inverted T wave became more shallow (Fig. 4). As for the therapy,
Figure 3. Ventricular fibrillation induced by catheter manipulation in the right ventricular outflow tract.

Discussion

Since the new clinical entity of Brugada syndrome was introduced in 1992, numerous reports on the acquired form of Brugada syndrome have also been published. Those have included an acquired form of Brugada syndrome caused by 1) drugs such as Na channel blockers, Ca channel blockers, beta blockers, K channel openers, psychiatric drugs, cocaine intoxication, alcohol intoxication, 2) electrolyte abnormalities such as hyperkalemia and hypercalcemia, 3) acute ischemia, 4) increased insulin levels, 5) hyperthermia, and 6) hypothermia (1). Among those reports, there has been only one report regarding histamine H1 receptor antagonists (2). In that paper on a case of asymptomatic Brugada syndrome in which an infusion of dimenhydrinate, a first generation antihistamine, caused a coved-type ST segment elevation in leads V1 and V2, the ECG recordings obtained on the following day and one month later showed no Brugada type ECG. The authors stated that the mechanism underlying the Brugada-type ECG change induced by dimenhydrinate, was probably due to the drug’s anticholinergic action and a mild to moderate local anesthetic effect via a sodium channel blockade in the inactivated state.

It has been reported that promethazine, a competitive antagonist of the H1 histamine receptors, blocks the cardiac Na channels in a manner similar to that of the class I antiarrhythmic agents and that drug possesses a characteristic of slow recovery of the Na channels from inactivation in guinea pig ventricular myocytes (4). Other experimental findings have also suggested that promethazine induces electrophysiological alterations and antiarrhythmic properties in the myocardium (5-7). Moreover, a recent study showed that brompheniramine, a first generation histamine H1 antagonist, inhibits the human ether-a-go-go-related gene (hERG) K+ channels, sodium channels and calcium channels (8), suggesting that there is a possibility that antihistamine may cause Brugada-type ECG changes.

In the present case, four different kinds of antihistamines and antiallergenic drugs, all of which possess a histamine receptor blocking action were used. It has been demonstrated that a daily or seasonal difference in the Brugada ECG pattern in the right precordial leads is usually observed in this syndrome. In our case, a daily or seasonal difference in the ECG pattern in the right precordial leads was also observed to some degree. However, as shown in Figs. 4, 5, the Brugada type ECG changes became augmented after starting those antihistamines and they regressed after discontinuing those drugs, and hence, it was considered that the antihistamines may have played a major role in those Brugada-type ECG changes. Although the effects of each agent on the cardiac ion channels has not yet been proven, it was speculated that the enhancement of the Brugada-type ECG changes in

an ICD implantation was selected for the patient since ventricular fibrillation was induced and he had a family history of sudden cardiac death. After 20 months of follow-up, the patient has been asymptomatic without any medical therapy including antihistamines or antiallergenic drugs.
our case was possibly caused by the class I, III, and IV antiarrhythmic actions of the antihistamines based on the report as described above.

It is well known that antiallergenic drugs may cause QT prolongation, which is possibly caused by the cardiac potassium current $I_{Kr}$-blocking action (9, 10), and hence, we usually take special precautions when using those drugs in patients with a long QT interval. In our case, although four different kinds of antihistamines and antiallergenic drugs were prescribed and those were speculated to have an additive effect, it suggested that we should also pay special attention to the ECG changes and symptoms when we have to prescribe antihistamines or antiallergenic drugs for patients with Brugada syndrome.

**Limitations**

Since daily or seasonal differences in the Brugada ECG pattern in the right precordial leads is usually found in this syndrome, we should have tried to examine the reproducibility of those drugs on the ECG changes in this case. However, informed consent could not be obtained from the patient since it was a provocative test and there was a risk of inducing ventricular arrhythmias, and furthermore, his eczema was almost cured by another treatment (topical treatment). Further studies including cellular and clinical electrophysiological studies will be required to clarify the possible
Figure 5. ECG changes before and after starting the antihistamines.

interactions of the antihistamines and Brugada-type ECG changes.

References