Nitrate Tolerance as a Possible Cause of Multidrug-Resistant Coronary Artery Spasm

A Case Report and Its Implications

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Summary

Coronary spasm can usually be controlled by administration of Ca antagonists. However, there are some cases of coronary spasm whose attacks cannot be controlled even with large doses of Ca antagonist and/or its combination with nitrates. Here we describe the case of a 41-year-old man whose attacks of coronary spasm were resistant to the combined administration of nitrates, Ca antagonists, and a statin. The attacks were alleviated and disappeared after withdrawal of nitrates and recurred after readministration of a nitroglycerin patch. The involvement of nitrate tolerance in the pathogenesis of multidrug resistant coronary spasm was revealed and its implication discussed. (Int Heart J 2010; 51: 211-213)

Key words: Alcohol, Aldehyde dehydrogenase 2, Coronary spasm, Nitrate tolerance

Coronary artery spasm plays an important role in the pathogenesis of not only variant angina but also coronary heart disease (CHD) in general, including unstable angina, acute myocardial infarction, and sudden death. Organic nitrates including glyceryl trinitrate (GTN) or isosorbide dinitrate (ISDN) have been widely used for the treatment of CHD and the attack of coronary spasm is usually promptly relieved by sublingual administration of GTN or ISDN. A major therapeutic limitation inherent to organic nitrates, however, is the development of tolerance which occurs during chronic treatment with these drugs. Recent studies have shown that mitochondrial aldehyde dehydrogenase (ALDH2) plays a central role in the development of nitrate tolerance. Ca antagonists are, therefore, the first choice for the treatment of coronary spasm. There are, however, not a few cases of coronary spasm whose attacks cannot be controlled even with high doses of Ca antagonists or combination of these agents. Long-acting nitrates are often added in the management of such cases. We report a case of multidrug resistant coronary spasm whose attack ameliorated on withdrawal of chronic administration of nitrates and deteriorated on continued GTN medication. This report was approved by the ethical committee of our hospital and written informed consent was obtained from the patient.

Case Report

A 41-year-old Japanese man was referred to our hospital because of frequent episodes of constriction in the neck in the early morning. His medical history was unremarkable except for an episode of acute alcohol intoxication and the “flushing response” to alcohol. He had smoked 20 cigarettes a day for 25 years until 1 year previously, when an atrial septal defect (ASD) was detected and he had an Amplatzer device placed for closure of ASD. One month thereafter, he noticed the episode of constriction of the neck in the early morning. Ambulatory monitoring of an electrocardiogram (ECG) revealed ST segment elevation on the inferior leads during the attacks and he was put on the Ca antagonist benidipine (8 mg/day) and the statin pravastatin (5 mg/day) at a local hospital. However, the attacks could not be controlled, occurring 3-4 times a week for 2 months. A GTN patch (10 mg/day) and nicorandil (5 mg/day) were then added and the attacks were alleviated for several days. However, the attacks gradually increased in frequency and severity, occurring even during daytime 4-10 times every day, often unresponsive to several oral sprays of GTN over 5 months before the admission. His medications included GTN tape (20 mg/day), slow-release ISDN (60 mg/day), benidipine (8 mg/day) or diltiazem (200 mg/day), nifedipine (40 mg/day), nicorandil (15 mg/day), fluvastatin (20 mg/day), atenolol (25 mg/day), and magnesium oxide (750 mg/day) on admission. He thus had multidrug-resistant angina and was referred to our hospital. Physical examination on admission was normal with a blood pressure of 102/69 mmHg, pulse of 75 beats/minute, and temperature 36.4°C Other than the presence of an Amplatzer device for closure of ASD, no ECG, chest radiograph, or echocardiogram abnormalities were
detected. His laboratory values were also normal except for a serum triglyceride level of 209 mg/dL. After admission, all the antiangina drugs except benidipine (8 mg/day) were withdrawn. The spontaneous attacks then gradually decreased and disappeared completely on the 4th hospital day. The attacks were induced by intracoronary injection of ACh at CAG on the 5th hospital day and by hyperventilation test on the 6th hospital day. To elucidate the possible role of nitrate tolerance, the examination of FMD as well as ECG monitoring was performed before and after GTN patch (20 mg/day) for 3 days. The attacks increased in frequency associated with decreased FMD with continuous GTN application. ACh indicates acetylcholine; CAG, coronary angiography; FMD, flow mediated dilatation; GTN, glyceryl trinitrate; and ISDN, isosorbide dinitrate.

**Figure 1.** Time course of the attacks in relation to the medications and FMD. After admission, all antiangina drugs except benidipine (8 mg/day) were withdrawn. The spontaneous attacks then gradually decreased and disappeared completely on the 4th hospital day. The attacks were induced by intracoronary injection of ACh at CAG on the 5th hospital day and by hyperventilation test on the 6th hospital day. To elucidate the possible role of nitrate tolerance, the examination of FMD as well as ECG monitoring was performed before and after GTN patch (20 mg/day) for 3 days. The attacks increased in frequency associated with decreased FMD with continuous GTN application. ACh indicates acetylcholine; CAG, coronary angiography; FMD, flow mediated dilatation; GTN, glyceryl trinitrate; and ISDN, isosorbide dinitrate.

**Figure 2.** Coronary angiographic and electrocardiographic findings during the attacks and after administration of GTN. Severe spasm of the RCA and LCA associated with ST segment elevation on ECG was induced by intracoronary injection of 20 μg and 50 μg of ACh, respectively, and disappeared after GTN administration. ACh indicates acetylcholine; ECG, electrocardiogram; GTN, glyceryl trinitrate; LCA, left coronary artery; and RCA, right coronary artery.

**Figure 3.** Twelve-lead electrocardiogram of hyperventilation test. Hyperventilation test induced attacks with ischemic ST segment changes in leads II, III, aVF, V5, and V6 on ECG.

**DISCUSSION**

Organic nitrates including GTN have been widely used for the treatment of coronary heart disease. GTN releases NO or NO congener in vivo and relaxes vascular smooth muscle. A major therapeutic limitation inherent to organic nitrates is the development of tolerance in chronic treatment. Recent studies have shown that the activation of ALDH2 reduces ischemic damage to the heart and that reactive oxygen species formation and a subsequent oxidative inactivation of ALDH2 play a central role in the development of nitrate tolerance, leading to endothelial dysfunction. We have shown that endothelial dysfunction or deficient NO bioactivity is essential in the pathogenesis of coronary spasm. ALDH2 also plays a central role in the metabolism of alcohol (ethanol), catalyzing the oxidation of ethanol derived acetaldehyde to acetate. Approximately 40% of the East Asian population has a polymorphism of ALDH2, ALDH2*1/2 allele.
is inherited as an autosomal dominant trait. It is known that the “flushing response” to alcohol is an indicator of the ALDH2*2 allele and we have reported that patients with “flushing response” are more likely to suffer from coronary spasm. It is interesting to note in this connection that this patient had an ALDH2*2 allele and the “flushing response” to alcohol and that chronic treatment with nitrates (GTN, ISDN, and nicorandil) added to Ca antagonists (nifedipine, diltiazem, benidipine) and statins (pravastatin, fluvastatin) resulted in deterioration of the attacks. FMD as a marker of endothelial function decreased on continued administration of GTN, indicating that endothelial function deteriorated on chronic nitrate treatment. The deterioration of endothelial function is thus considered to have led to the aggravation of the attacks. Intriguingly, there is evidence that long-term nitrate therapy increases cardiovascular mortality.

We conclude that continuous administration of nitrates should be avoided in patients with coronary spasm, particularly in those with “flushing response” to alcohol.

REFERENCES