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Short Communications

Vasospastic Angina Induced by Nonsteroidal Anti-Inflammatory Drugs

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Summary: We report two cases of vasospastic angina associated with anaphylactic reaction caused by nonsteroidal anti-inflammatory drugs (NSAIDs). Both patients exhibited anaphylactic manifestations, such as general rash and urticaria, along with angina pectoris with electrocardiographic ST-segment elevations after suppository administration of diclofenac sodium or indomethacin, the most commonly used NSAIDs. Although these patients had normal coronary arteriograms, intracoronary administration of ergonovine or acetylcholine provoked diffuse coronary artery spasms accompanied by chest pain and ischemic ST-segment changes. It is therefore suggested that an allergic mechanism may be involved as a causative factor of the coronary artery spasm induced by NSAIDs.

Key words: vasospastic angina, anaphylactic reaction, diclofenac sodium, indomethacin

Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used, but, though rare, have many adverse effects including gastrointestinal toxicity, renal failure, hematological disorders, hepatotoxicity, and anaphylactic reaction.[1] In this report, we describe two cases of vasospastic angina associated with anaphylactic reaction caused by diclofenac sodium and indomethacin, the most commonly used NSAIDs.

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Case Report

Case No. 1

The patient was a 69-year-old man who was admitted to our hospital for coronary arteriography following a previous episode of chest pain. Seven weeks before admission, he had suffered from chest pain with ischemic ST-segment changes following suppository administration of diclofenac sodium (25 mg), an NSAID, used for the relief of algos after surgery for osteomyelitis. He had no history of allergic factors or major risk factors for coronary artery disease. Physical examination, chest roentgenogram, electrocardiogram (ECG), and two-dimensional echocardiogram were normal. No significant ST-segment changes were observed at a peak heart rate of 151 beats/min during exercise testing. During hospitalization, because of fever (38°C), suppository diclofenac sodium (12.5 mg) was administered. Five minutes later, the patient developed various symptoms and signs including chest pain, dyspnea, vomiting, excessive sweating, and general rash with itching. Systolic blood pressure and pulse rate dropped to 60 mmHg and 48 beats/min, respectively. Significant ST-segment elevations in leads II, III, aVF, V_5, and V_6 with 2:1 atrioventricular block were observed. Nitroglycerin (1 mg) and atropine sulfate (0.5 mg) were injected intravenously. After these injections, symptoms and signs improved and ST segments promptly returned to the baseline (Fig. 1). Coronary arteriography, which was performed 10 days after the cardiac event, showed normal coronary trees. An ergonovine provocation test showed severe spasm at the middle portion of the right (Fig. 2) and left coronary arteries accompanied by chest pain and ischemic ST changes. Intracoronary administration of isosorbide dinitrate (2.5 mg) promptly resolved those spasm, chest pain, and ST-segment elevations. His subsequent hospital course was uneventful with treatments with diltiazem (100 mg), long-acting nitrate (50 mg), and nicorandil (15 mg). In this case, because diclofenac sodium had not been recognized on admission as a cause of angina, it was accidentally (unintentionally) used as antipyretic treatment. As a result, we reproduced angina with ST-segment elevations caused by diclofenac sodium.

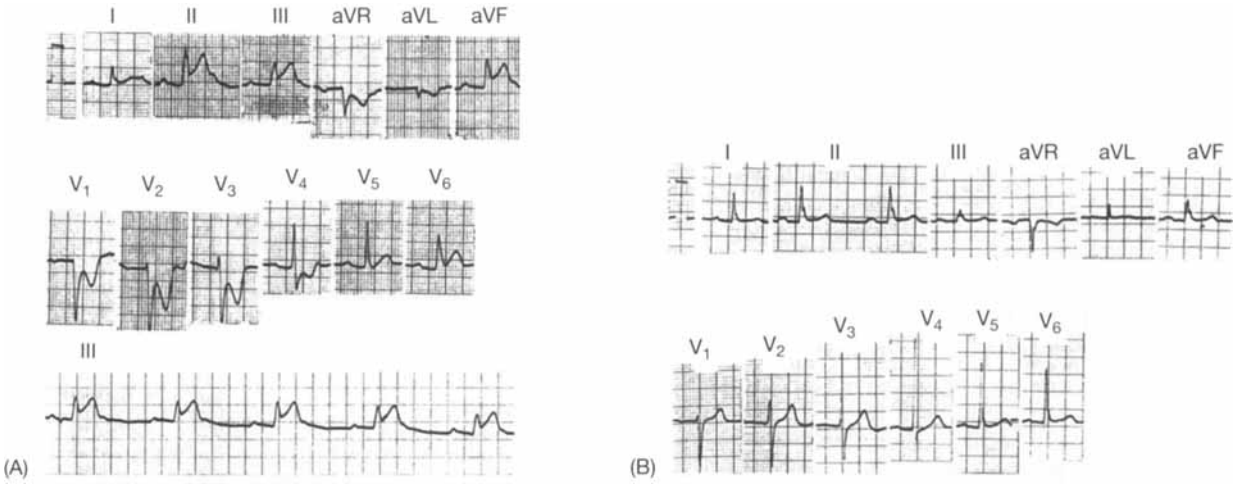

FIG. 1 Standard 12-lead electrocardiograms during an angina attack (A) and after intravenous injection of nitroglycerin (B).

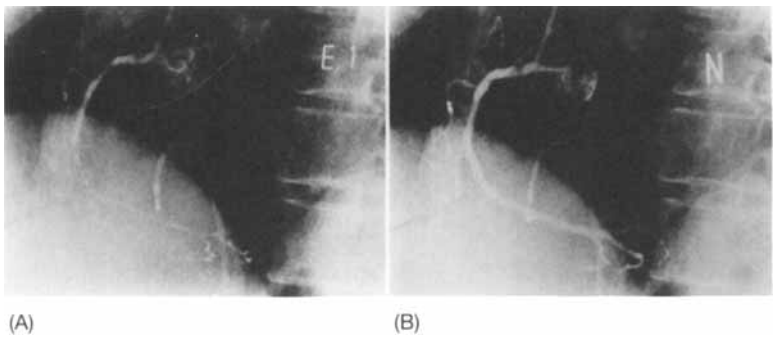

FIG. 2 Coronary arteriograms after intravenous injection of ergonovine (A) and after intracoronary administration of isosorbide dinitrate.

Case No. 2

The patient was a 74-year-old woman who had been treated for rheumatoid arthralgia with oral administration of indomethacin, an NSAID, for 12 years without any side effects. She had no history of major coronary risk factors, but a history of bronchial asthma. Recently, she developed urticaria after suppository administration of indomethacin (50 mg). One month later, she was admitted to our hospital by ambulance because she developed fatigue, urticaria, chest pain, and syncope following suppository administration of indomethacin (50 mg). Physical examination revealed systolic blood pressure of 50 mmHg and regular pulse at 50 beats/min, and ECG showed significant ST-segment elevations in leads II, III, and aVF with 2:1 atrioventricular block. Within 5 min after sublingual administration of nitroglycerin, symptoms and ECG abnormalities disappeared (Fig. 3). Although coronary arteriography performed 20 days after admission showed normal coronary arteries, intracoronary administration of ergonovine or acetylcholine provoked diffuse spasms in the right (Fig. 4) and left coronary arteries, accompanied by chest pain and ischemic ST-segment changes. In this case, other NSAIDs including diclofenac sodium, which were tested to prepare for her future treatment for rheumatoid arthralgia, produced no chest pain or ischemic ST changes.

Discussion

Since it was not ethically feasible to perform provocation tests by these NSAIDs during coronary arteriography, NSAIDs-induced coronary spasm was not angiographically demonstrated in these cases. Both patients had normal coronary arteriograms, and intracoronary administration of ergonovine or acetylcholine provoked coronary spasms accompanied by chest pain and ischemic ECG changes. Because similar chest pain and ischemic ECG changes were observed during the cardiac events induced by NSAIDs and because, in the first case, administration of diclofenac sodium induced chest pain and ischemic ST-segment change reproducibly, it is plausible that NSAIDs induced coronary spasm in these patients. Furthermore, the strictly temporal relationship between the ECG changes and anaphylactic manifestations observed in our patients strongly suggests that these cardiac

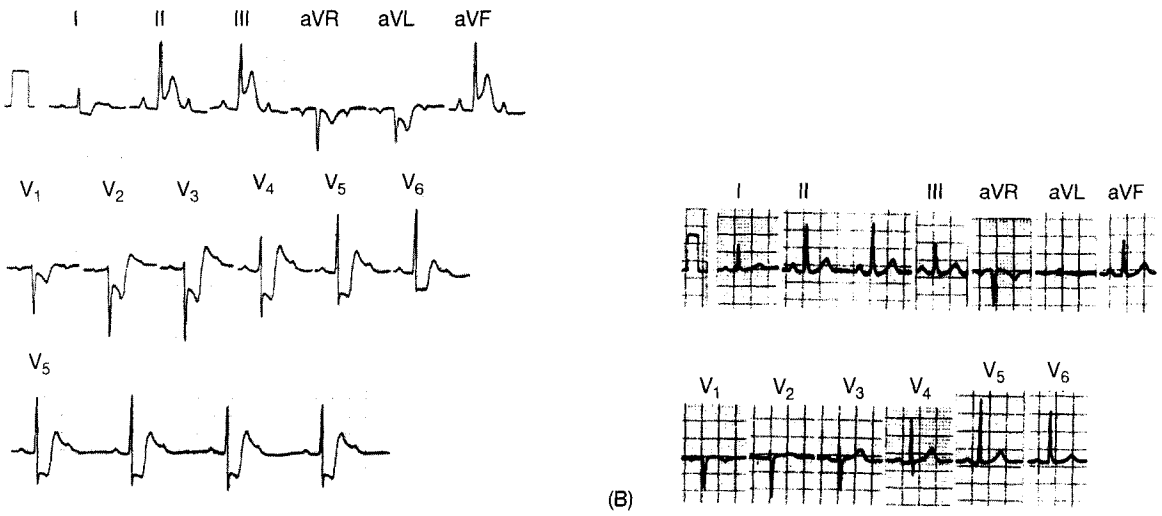

FIG. 3 Standard 12-lead electrocardiograms during an angina attack (A) and after sublingual administration of nitroglycerin (B).

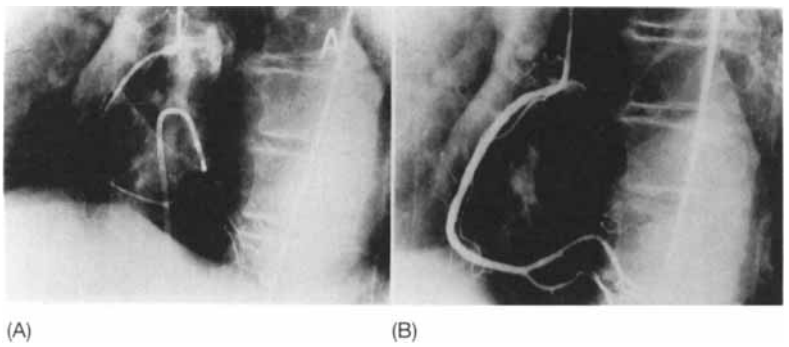

FIG. 4 Coronary arteriograms after intravenous injection of acetylcholine (A) and after intracoronary administration of isosorbide dinitrate (B).

events were related to the allergic reaction. Forman *et al.* reported that more mast cells were found in the adventitia of the involved artery in a patient with coronary spasm than in those without coronary spasm and suggested that mast cell-secreted vasoactive substances including histamine and serotonin may play an important role in the pathogenesis of coronary spasm.[2] Indeed, it has been reported that exogenously administrated histamine or serotonin causes coronary vasoconstriction in patients with vasospastic angina.[3,4] Vasocon-striction caused by inhibition of vasodilatory prostaglandins such as PGI_2 could also be a cause of coronary spasm. However, since other NSAIDs produced no chest pain and/or ischemic ST changes in the second case, the possibility is unlikely in this case. Although there have been reports of coronary vasospasm induced by steroid[5] and contrast medium,[6] we believe that this is the first report of vasospastic angina induced by NSAIDs.

Conclusion

We report two cases of vasospastic angina probably induced by nonsteroidal anti-inflammatory drugs. Because these drugs are commonly used, they should be administered with caution.

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