



Letter to the Editor

Hypersensitivity to proton pump inhibitors: Lansoprazole-induced Kounis syndrome

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Abstract

Proton pump inhibitors are commonly used in clinical practice for the treatment of peptic ulcer and gastroesophageal reflux and are well tolerated by the patients. Their use is rarely associated with hypersensitivity and anaphylactic reactions. According to the reports in the Uppsala Monitoring Center database the frequency of hypersensitivity reactions out of all reported adverse reactions for proton pump inhibitors and H₂-histamine receptor antagonists was between 0.2% and 0.7%. A few cases of hypersensitivity to lansoprazole have been reported. We report a patient who developed Kounis syndrome after taking 30 mg of lansoprazole. This is the first report of Kounis syndrome associated with lansoprazole administration in the world literature.

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1. Introduction

Proton pump inhibitors are the main substances currently used for the treatment of various gastrointestinal disorders. In cardiac patients they are usually administered in conjunction with aspirin administration. They are non-competitive inhibitors of the parietal cell membrane enzyme H⁺/K⁺ adenosine triphosphatase. This enzyme acts as “acid pump” or “proton pump” which constitutes the final stage of the hydrochloric acid secretion in the stomach. They are metabolized in the liver via cytochrome P450. Their use is rarely associated with site effects and especially with

hypersensitivity reactions. The following report is of a patient who developed urticarial reaction after ingesting 30 mg of lansoprazole and immediately after an acute inferior allergic myocardial infarction [1–4].

2. Case report

A 52 year old man was transferred to the emergency department of our hospital complaining of generalized itching, malaise, shortness of breath, difficulty in swallowing, and abdominal pain and numbness in all over the body. On examination he had erythematous rash covering the whole body with facial oedema, he was sweating, pale, and agitated. His symptoms started 10 min after taking 30 mg of lansoprazole for his abdominal pain. He gave a history of previous peptic ulcer and hematemesis and was taking occasionally various antileptic preparations including

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omeprazole and ranitidine with good tolerance. He was non-smoker without any previous personal or family history of allergy or other drug sensitivity. His blood pressure was 110/80 mmHg. The pulse 81 beats/min regular and the electrocardiogram was within normal limits (Fig. 1A). Pulse oxymetry showed an oxygen saturation of 92%. He was treated with 500 mg of hydrocortisone sodium succinate and 4 mg of dimetridene intravenously as well as inhaled corticosteroid for the difficulty in breathing.

However, while he was on the emergency room, he suddenly developed severe retrosternal pain radiating to both arms and started vomiting. A second electrocardiogram (Fig. 1B) showed elevation of ST segment in II, III, AVF, V₃–V₅ leads compatible with acute inferior myocardial infarction. His blood pressure dropped to 80/60 mmHg. At that time the patient was given a second bolus of 500 mg of hydrocortisone sodium succinate IV, 10 mg morphine sulphate and blood was taken for cardiac enzymes, troponins, histamine, tryptase, IgE immunoglobulins, complement protein and blood count. Afterwards, the patient was admitted to the coronary care unit where he was thrombolized with tenecteplase bolus of 7000 IU. His symptoms gradually subsided during the following 24 h and the

electrocardiographic changes returned to normal (Fig. 1C). Echocardiographic examination performed at bedside revealed hypokinesia of the inferior wall with an estimated ejection fraction of 50%. The results of blood examination showed increased troponin T of 1.5 ng/mL (normal range <0.1 µg/L) and peak creatinine kinase of 1342 IU/L with CPK-MB of 150 IU/L. Blood eosinophils were raised to 9% but the complement proteins C3 and C4 were normal. Other measurements were increased as follows: serum tryptase 20, 35, 15 µg/L at 1, 2, 3 h respectively (normal range 5.6–13.5), histamine 0.9 ng/L (normal range <0.2), immunoglobulin IgE 190 IU/mL (normal range <110).

Treadmill stress test and hyperventilation test were normal.

We did not proceed to oral test dose with lansoprazole because in the view of the acute myocardial infarction this could be clinically unsafe. However we performed skin prick tests with lansoprazole (30 mg in 1 mL saline) which produced a wheal of 3 mm at 20 min and with omeprazole (20 mg in 1 mL saline), pantoprazole (20 mg in 1 mL saline), ranitidine (50 mg in mL saline) and buffered saline which produced no reaction, thus confirming only lansoprazole hypersensitivity.

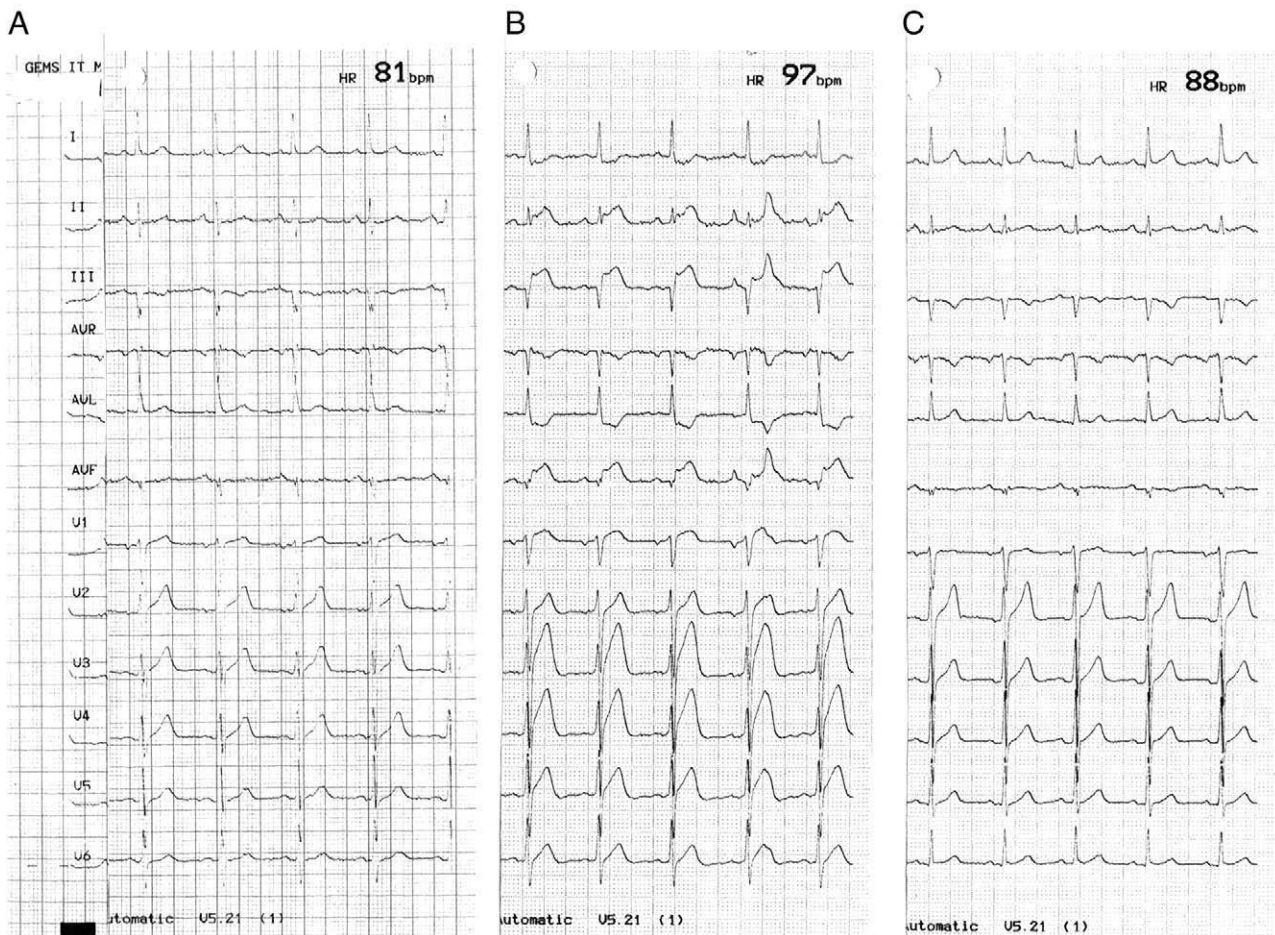


Fig. 1.

The patient was discharged on the seventh day of admission. Coronary angiography in the neighbouring University hospital showed 90% right coronary artery lesion and he underwent successful stenting.

3. Discussion

The described patient is the first to develop acute myocardial infarction following an allergic reaction after ingestion of lansoprazole medication. There are various drugs capable to induce Kounis syndrome [5] and include antibiotics, analgesics, antineoplastics, contrast media, intravenous anesthetics, corticosteroids, non-steroidal anti-inflammatory drugs, thrombolytics and skin disinfectants. Few proton pump inhibitors used in everyday practice have been incriminated in rare occasions to induce hypersensitivity reactions. The older preparations omeprazole [6–10], lansoprazole [11–14] and pantoprazole [15–17] have all been, although rarely, associated with hypersensitivity reactions. A recent literature review [14] has shown that only the newest proton pump inhibitors rabeprazole and esomeprazole are free, so far, of such reactions. Cross-reactivity between the various brands has been also reported [12].

The proton pump inhibitors are modified benzimidazoles containing the pyridine ring and they differ to each other in the substitution chains. They act by increasing the intragastric pH levels, which may enhance the effectiveness of the local immune response, reduce the washout of antibiotics from the gastric mucosa, and lower the minimal inhibitory concentrations of pH-sensitive antibacterial agents [10].

Our patient experienced an episode generalized urticaria after oral intake of lansoprazole which was followed by acute anterior myocardial infarction. The clinical presentation, the positive skin prick tests to lansoprazole, the elevated IgE concentrations, and the raised serum histamine and tryptase levels suggest that an IgE mediated mechanism was involved in both reactions, namely, urticaria and acute myocardial infarction. During hypersensitivity reactions vasoconstricting and collagen-degrading compounds are released locally and in peripheral circulation from activated mast cells. Preformed mediators such as, histamine, chymase, tryptase, neuropeptides, and proteoglycans, as well as newly synthesized mediators such as arachidonic acid products, an array of chemokines and cytokines, and platelet activating factor are some of them. Clinical and experimental studies [18] have shown that these mediators can induce coronary artery spasm and/or acute myocardial infarction. In particular, histamine is raised in the coronary circulation of patients with variant angina and can induce tissue factor expression. Tryptase has been implicated in acute coronary syndromes and can degrade HDL. Indeed, tryptase and histamine were

elevated in the serum of the described patient during the hypersensitivity reaction and the following acute myocardial infarction.

This report shows that the proton pump inhibitor lansoprazole can induce allergic myocardial infarction and should be added in the list of drugs capable to induce Kounis syndrome. Since cross-reactivity between these agents has been proven, physicians should be aware of this dangerous association and should always think about Kounis syndrome when they treat hypersensitivity complications induced by any of the above compounds.

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