Severe adverse reactions caused by omeprazole: A case report

MEILING YU[1,2*], JIANGHUA QIAN[3*], DAOHUA GUO[1], LI LI[4] and XIAOLIN LIU[2]

Departments of [1]Pharmacy and [2]Neurology, The First Affiliated Hospital of Bengbu Medical College, Bengbu, Anhui 233004; [3]Faculty of Pharmacy, Bengbu Medical College, Bengbu, Anhui 233030, P.R. China; [4]Lung Biology Laboratory, Department of Medicine, Division of Pulmonary, Allergy and Critical Care, Columbia University Medical Center, New York, NY 10032, USA

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Abstract. A 61-year-old female patient was admitted to hospital following development of a whole-body rash for 10 days, diarrhea for 7 days, and unconsciousness and oliguria for 1 day. The patient had developed stomach discomfort following the oral administration of non-steroidal anti-inflammatory drugs, the exact nature of which was unknown, for the treatment of arthritic pain for >1 month. The patient was then prescribed omeprazole enteric-coated tablets (20 mg twice daily) for treatment of this symptom. However, the patient developed a whole-body rash 7 days after administering omeprazole, 10 days prior to admission. This symptom was followed by severe diarrhea with nausea and vomiting after 10 days, then shock. The shock occurred after administering omeprazole for 16 days. The patient developed a whole body rash 7 days after administering omeprazole, then 3 days later (after administering omeprazole for 10 days) severe diarrhea with nausea and vomiting occurred. The shock remained until administering omeprazole on the 16th day, with severe diarrhea with nausea and vomiting occurring 6 days later. The patient's condition did not improve following treatment for allergies, low blood pressure and oliguria in the Intensive Care Unit (ICU) department at Suzhou Municipal Hospital. For further diagnosis and treatment, the patient was admitted to the ICU department of The First Affiliated Hospital of Bengbu Medical College and was given a fluid infusion, antibiotics and phlegm-reducing treatment, a plasma infusion, blood filtration, and anti-diarrheal and anti-allergy treatment. The patient's vital signs were stable, with a normal temperature and hemogram results, and improved kidney function and deflorescence. Genetic screening revealed that the patient poorly metabolized omeprazole. Therefore, severe adverse reactions (allergic shock, rash and diarrhea) experienced by the patient were caused by the accumulation of omeprazole metabolites resulting from its slow metabolism *in vivo*.

Correspondence to: Professor Xiaolin Liu, Department of Neurology, The First Affiliated Hospital of Bengbu Medical College, 287 Changhuai Road, Bengbu, Anhui 233004, P.R. China
E-mail: liuxiaolin1888@sohu.com

*Contributed equally

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Introduction

Omeprazole is one of the most commonly clinically used proton pump inhibitors (PPIs), which can selectively and non-competitively inhibit the H^+/K^+-ATP enzyme in parietal cell membranes, and can act for 24 h for lasting effects (1,2). It is widely used in the clinic for the treatment of peptic ulcer, gastroesophageal reflux disease, Zollinger Ellison syndrome, infections caused by *Helicobacter pylori*, gastrointestinal bleeding and nonsteroidal anti-inflammatory drug-induced gastric mucosal injuries (2-6).

A number of adverse reactions caused by omeprazole have been reported, including allergic reactions, tachycardia, alimentary tract hemorrhage, liver damage, leucopenia, mental disorders and joint pain (7-18). In the present study, a patient developed allergic shock, significant drug eruption and severe diarrhea following the oral administration of omeprazole. This report reminded doctors and pharmacists that pharmaceutical care of PPIs should be strengthened in future work.

Case report

A 61-year-old female was admitted to The First Affiliated Hospital of Bengbu Medical College (Bengbu, Anhui, China) on May 4, 2015 as a result of experiencing a whole-body rash for 10 days, diarrhea for 7 days, and unconsciousness and oliguria for 1 day. The patient had been diagnosed with hyperthyroidism 30 years ago, but was not administered a formal treatment or monitored. The patient had been experiencing arthritic pain for >1 month and had received an intra-articular injection and oral administration of non-steroidal anti-inflammatory drugs (NSAIDs), but the exact drug was unknown. The patient was prescribed 20 mg twice daily and orally of omeprazole enteric-coated tablets (ECT; Kaikaii Yuansheng Pharmaceutical Co., Ltd, Xinyang, China) to treat the stomach discomfort caused by these NSAIDs. However, the patient developed a whole-body rash 7 days after omeprazole administration, which was 10 days before admission. This rash did not disappear following anti-allergy treatment at a local clinic on April 24, 2015 (Fig. 1). The patient also experienced diarrhea

>10 times a day, and nausea and vomiting from 7 days prior to admission. The patient's diarrhea was treated with an infusion of unknown drugs 2 days prior to admission at the local Suzhou Municiple Hospital on May 2, 2015 but demonstrated no marked improvement in symptoms. The patient developed a high fever reaching 40˚C, 1 day prior to admission, and was transferred the Intensive Care Unit (ICU) to continue treatment for low blood pressure and oliguria. The patient was treated with 20 mg norepinephrine (Wuhan Yuanda Pharmaceutical Co., Ltd, Wuhan, China) intravenously once per day to treat low blood pressure, and furosemide injection (40 mg) was administered intravenously once per day to cure oliguria. Norepinephrine activates the alpha receptor, then induces the small artery and vein blood vessel to contract and thus increases the blood pressure. The patient lost consciousness and her condition did not improve following treatment for allergies and a fluid infusion of 20 mg norepinephrine was pumped into the blood intravenously once per day in order to increase blood pressure. Norepinephrine activates the α-receptor, then induces the small artery and small vein blood vessel to contract and finally increases the blood pressure.

The patient was then transferred to the ICU department of The First Affiliated Hospital of Bengbu Medical College on May 4, 2015 for further treatment as described below. A tracheal intubation with mechanical ventilation was performed due to the patient's loss of consciousness and dyspnea. Blood gas analysis revealed severe metabolic acidosis and electrolyte disturbance of pH 6.86, $PaCO_2$ 41 mmHg, PaO_2 120 mmHg, HCO_3^- 7.1 mmol/l, BE^- 26.1 mmol/l, Na^+ 134.7 mmol/l, K^+ 2.26 mmol/l and Ca^{2+} 0.93 mmol/l. Fluid infusion, correcting acid-base disturbance (by sodium bicarbonate injection) and other treatment, including calcium and potassium supplements, calcium gluconate injection (Yunan Baiyao Group Co., Ltd., Kunming, China) and potassium chloride injection (Hebei Kelun Pharmaceutical Group Co., Ltd., Xiantao, China). Admission examination results were as follows: Temperature, 37˚C; pulse, 117 times/min; respire, 34 times/min; blood pressure, 106/56 mmHg; and Glasgow score, 3 (19,20). The patient maintained a whole-body rash and did not respond to loud noise or physical stimuli, but did respond to pain stimulation induced by piercing with a needle, meaning that the central nervous system functioned normally. The patient's pupils measured 1 mm and did not react to light. The patient's breath sounded rough and rale upon lung auscultation as determined by a stethoscope, but was not obviously dry. Electrocardiogram monitoring (model DASH5000; GE Healthcare Life Sciences, Chalfont, UK) showed a regular sinus rhythm (heart rate, 117 beats/min) and no cardiac murmur. The abdomen was soft and the patient demonstrated no presence of pain when it was pressed. The liver and spleen were small enough to feel by doctors, implying that their function is normal, and bowel movement sounds could be heard. No obvious edema was observed in the four limbs, but the patient presented with oliguria. A routine blood test indicated that the patient's white blood cell (WBC) count had increased, and neutrophils (NEUTs) were not measured (WBC, $32.67x10^9$ cells/l; hemoglobin, 127 g/l; hematocrit, 34%; platelet, $386x10^9$ platelets/l). The results led to the following symptom identification: i) Allergic shock; ii) pulmonary infection and respiratory failure; iii) acute kidney injury; iv) metabolic acidosis; v) electrolyte disturbance, hypokalemia and hypocalcemia; vi) hyperthyroidism; and vii) diarrhea.

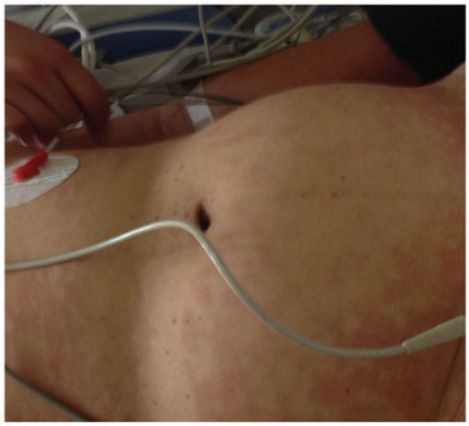

Figure 1. Skin rashes on the patient.

The patient was administered 500 ml glucose and sodium chloride injection and 500 ml polygeline injection both intravenously. A total of 20 mg norepinephrine was also administered intravenously by a drip once per day in order to maintain blood pressure. 2.25 g piperacillin sodium (Haerbin Pharmaceutical Group Co., Ltd, Haerbin, China) and tazobactam sodium (Haerbin Pharmaceutical Group Co., Ltd) were both administered intravenously three time per day for antibiotic treatment upon admission to the ICU of The First Affiliated Hospital of Bengbu Medical College on May 4th. In addition, blood filtration was performed for acute kidney injury, 3.0 g calcium gluconate injection once daily and 6.0 g 10% potassium chloride injection once daily were administered to treat electrolyte disturbance, hypokalemia and hypocalcemia. Furthermore, 6.0 g montmorillonite powder (Hunan Fangsheng Pharmaceutical Group Co., Ltd., Changsha, China) was injected through the nose three times a day and 2.0 g triple viable *Bifidobacterium lactobacillus* (Shanghai Xinyi Pharmaceutical Group Co., Ltd., Shanghai, China) were administered through the npse three times a day in order to treat diarrhea and regulate intestinal flora. Loperamide hydrochloride (Xian Janssen Pharmaceutical Ltd., Hefei, China) capsules at 4.0 g were administered through the nose once per day to inhibit intestinal motility, as the patient was experiencing diarrhea >10 times a day. Furthermore, an injection of 80 mg methylprednisolone sodium succinate (Belgium Pharmacia The Upjohn Company, Shanghai, China) was administered intravenously once per day and 80 mg compound ammonium glycyrrhetate S (Jincheng Haisi Pharmaceutical Group Co., Ltd., Jincheng, China) was administered intravenously once per day for anti-allergy treatment. The patient was diagnosed with diarrhea, allergic shock caused by omeprazole, and omeprazole enteric-coated tablet-induced rash following a consultation between the Departments of Pharmacy and Gastroenterology on May 5th. Blood gas analysis on May 7th demonstrated a blood pH 7.48, $PaCO_2$ 35.5 mmHg, PaO_2 61.5 mmHg, BE 2.9 mmol/l, Na^+ 142.3 mmol/l, K^+ 3.42 mol/l and LAC 2.3 mmol/l. The patient's metabolic acidosis had been treated, but lactic acid levels remained high, which highlighted that there remained an obstruction to circulatory function, and a poor oxygenation index of ~100 mmHg. A

routine blood test on May 7th returned the following results: WBC, $9.49x10^9$ cells/l; NEUT, 84.1%; red blood cell count, $3.79x10^{12}$ cells/l; hemoglobin, 119.00 g/l; hematocrit, 0.33; and platelet count, $72x10^9$ platelets/l. The routine blood test and body temperature (37.0˚C) revealed a significant attenuation of the infection; a sputum smear revealed dysbacteriosis, and diarrhea, and the patient was administered norvancomycin by a nasal tube. On May 8th, the patient demonstrated marked deflorescence and a normal urine output, which indicated a significant improvement in kidney function. The patient stopped experiencing diarrhea on May 13th, after which her condition began to stabilize. Genetic screening revealed that the patient had a poor metabolism of omeprazole. Therefore, the severe adverse reactions (omeprazole enteric-coated tablet-induced rash, diarrhea and allergic shock) experienced by the patient were hypothesized to be caused by the accumulation of omeprazole metabolites *in vivo*. Informed consent was obtained from the patient's family.

Discussion

In the current case, family members reported that the patient only experienced stomach discomfort following the oral administration of NSAIDs, and that the patient's severe adverse reactions described above developed after administering omeprazole. As the patient's symptoms significantly improved when the administration of omeprazole was discontinued and treatment for these symptoms was provided, this reveals a relationship between the severe adverse reactions and the administration of omeprazole. There are multiple reports describing allergic shock caused by omeprazole, the majority of which occur during the infusion of omeprazole in the clinic (1,3,4). However, to the best of our knowledge, a case of severe adverse reactions, in particular severe diarrhea (>10 times a day with a stool quantity of ~3000-5000 ml per day) following the oral administration of omeprazole has not been reported. The adverse reactions appeared 7 days after omeprazole was first administered, which suggests that these adverse reactions may be caused by the accumulation of omeprazole metabolites *in vivo*. Research has demonstrated that the pharmacokinetics of omeprazole *in vivo* is primarily determined by the cytochrome P450 2C19 (*CYP2C19*) gene. CYP2C19 proteins are divided into slow and fast metabolizers (21,22). If patients are slow metabolizers, it will lead to the accumulation of omeprazole metabolites *in vivo*, which induce adverse reactions (13,14). Based on this, genetic screening of the patient was performed, and it was revealed that the patient was a slow metabolizer of omeprazole. In more detail, cell and tissue fluorescence quantitative PCR was performed and CYP2C19 was affected. This result verifies the speculation that the severe adverse reactions experienced by the patient were caused by the accumulation of omeprazole metabolites *in vivo*.

In the clinic previously, a patient presented with dermatitis exfoliativa ~1 month after being administered lansoprazole and esomeprazole on an alternate basis (23). All of these other rare and severe adverse reactions mentioned in the present study following administration of PPIs highlight that clinicians, in particular clinical pharmacists, must carefully regulate pharmaceutical treatment with PPIs. In recent years, with the increasing use of PPIs, a number of novel severe adverse reactions are being gradually discovered (15-18,23). In particular, the overuse of PPIs in the clinic has become problematic (24-26). A review of PPI prescriptions by pharmacists revealed that the primary reasons underlying PPI overuse are its prescription to patients who should not take it, excessive dosing frequencies and long treatment duration (26).

If PPIs are not used reasonably it may cause a series of consequences, including adverse reactions and drug resistance. If PPIs are used reasonably by the doctors. the life cycle of the drug can be extended. The regulated use of PPIs mainly depends on the following two aspects: Whether the clinicians can judge the therapeutic effects accurately; and whether the dosage regimen utilised by clinical pharmacists is appropriate. Due to the current lack of specific and detailed clinical guidelines regarding PPIs, clinicians and pharmacists should develop and optimize PPIs using certain criteria that will gradually aim at solving the main problems with usage of PPIs in the hospital. Pharmacists master the therapeutic indications of PPIs accurately in cooperation with physicians and pay attention to pharmaceutical care. The clinical application of PPIs should be monitored and performed as follows: PPIs should be administered as a short course of treatment; de-escalation therapy of acid inhibition should be used specifically; the usage of PPIs should be based on the results of gastroscopy examination; and regular risk assessment should be used if the PPI treatment duration is long. De-escalation therapy of acid inhibition means that PPIs are used for several weeks to inhibit gastric acid secretion, then H2-receptor blocking drugs such as ranitidine and famotidine should be used to continue inhibiting gastric acid secretion. Alternatively PPIs are given intravenously following oral administration. According to the gastroscopy results, duodenal ulcer, gastric ulcer, gastric mucosal injury and chronic gastritis are favorable for PPI use. If these recommendations are carefully followed by medical staff, patients may benefit from the use of PPIs.

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