Anaphylactic Reactions to Proton-Pump Inhibitors

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OBJECTIVE: To report two cases of anaphylactic reactions to proton-pump inhibitors (PPIs).

CASE SUMMARIES: A 54-year-old woman who had taken omeprazole in the past was treated with omeprazole 40 mg and developed periorbital edema, edema of the skin, pruritus, nausea, and vomiting about 45 minutes after taking one capsule. Five months later, she was treated with lansoprazole 30-mg capsules. Again, within 45 minutes she developed an even more serious reaction, with pruritus and urticaria on her whole body, increased sweating, facial edema, and loss of consciousness. A 61-year-old man took one tablet of pantoprazole 40 mg one year after first being treated with the drug. Within hours after ingestion, he developed malaise, generalized pruritus and urticaria, a swollen tongue and eyes, and diffuse sweating; his blood pressure decreased to 75/50 mm Hg.

DISCUSSION: Because of the acute onset of symptoms and close temporal association with exposure to the drug, as well as previous exposure to it, the reactions can be classified as anaphylactic shock to PPIs. These benzimidazole derivatives are chemically related; observations in a few patients, such as the first case above, suggest that cross-sensitivity may occur. The Uppsala Monitoring Centre (UMC) has received a total of 42 reports of anaphylactic reactions or anaphylactic shock in association with PPIs. These reports account for 0.2% of the total of reported suspected adverse drug reactions to PPIs, compared with 0.8% anaphylactic reactions in the UMC database as a whole.

CONCLUSIONS: These findings suggest that the chemically related PPIs can, as a group, cause anaphylactic reactions; however, the rate is comparatively low. Since anaphylaxis is a potentially serious reaction, more precise information is needed regarding its frequency, and healthcare professionals need to be aware of this possibility when prescribing these agents.

KEY WORDS: proton-pump inhibitors, anaphylactic reaction.

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Since the introduction of omeprazole, a proton-pump inhibitor (PPI), in 1988, PPIs have been widely used for the treatment of dyspepsia. To date, approximately four cases of anaphylactic reactions to PPIs have been reported in the literature.[1-4] The countrywide reporting system of the Netherlands Pharmacovigilance Foundation has received reports from general practitioners of two patients who had anaphylactic reactions after taking omeprazole, lansoprazole, and pantoprazole.

CASE REPORTS

CASE 1

A 54-year-old woman received a prescription for omeprazole 40-mg capsules from her general practitioner for peptic symptoms. About 45 minutes after taking the first capsule, she developed periorbital edema, edema of the skin, pruritus, nausea, and vomiting. After treatment with intravenous clemastine 2 mg, she recovered uneventfully. She had taken at least one, and probably more, omeprazole capsules in the past, according to the patient history. Because of persistent symptoms of dyspepsia, five months later it was decided to challenge her with lansoprazole 30-mg capsules under close monitoring of the general practitioner. Within 45 minutes, she developed an even more serious reaction than the first, with pruritus and urticaria on her whole body, increased sweating, facial edema, and loss of consciousness (blood pressure not measured). She recovered fully after she was treated with intravenous clemastine 2 mg. In both incidences, the patient did not take any other prescribed medication.

Author information provided at the end of the text.

CASE 2

A 61-year-old man with a history of coronary artery disease with repeated coronary angiography was treated with metoprolol, lisinopril, and isosorbide mononitrate. He received treatment for dyspepsia approximately one year earlier with pantoprazole 40-mg tablets prescribed by his general practitioner. Because of similar symptoms of dyspepsia, he decided to take one of the remaining pantoprazole tablets. Within hours following ingestion, he developed malaise, generalized pruritus and urticaria, a swollen tongue and eyes, and diffuse sweating. His blood pressure decreased to 75/50 mmHg (preexisting value not documented), and he was treated with intravenous clemastine and dexamethasone by a general practitioner on duty. After transport by ambulance to the hospital, the patient was monitored in the cardiology unit for several days; no further complications occurred, and the patient recovered fully.

Discussion

To our knowledge, our case is the first report of an anaphylactic reaction to pantoprazole published in the literature. Anaphylactic shock is classified as a sudden and substantial decrease of arterial blood pressure in close temporal association with exposure to a drug or other substance, which is not a vasovagal reaction and is not induced by a direct effect of a drug on cardiovascular function or hemodynamic regulation. Alternatively, the term anaphylactic shock may be used if clinical signs of shock such as hypotension, tachycardia or bradycardia, no heart rate, or loss of consciousness are present, or when one or both of the following groups of symptoms are also present: (1) itch-

ing, erythema, urticaria, angioedema and (2) laryngeal edema or spasm or bronchospasm.[5]

The acute onset of urticaria, edema, and hypotension or loss of consciousness and a close temporal association of these clinical signs with the ingestion of the tablets, as well as previous exposure to the drug, in both of our patients allows this reaction to be classified as anaphylactic shock, according to the Council for International Organizations of Medical Sciences.[5] The outcome of the causality assessment according to the Naranjo probability scale[6] was probable in all three observations (scores: patient 1, first drug: 7; patient 1, second drug: 7; patient 2: 6).

To date, four patients with anaphylactic reactions to PPIs have previously been described in the literature.[1-4] Ottervanger et al.[1] reported on a patient who developed an anaphylactic reaction within a few minutes following intravenous administration of omeprazole 40 mg. Six weeks before, this patient had developed urticaria while taking omeprazole 20 mg orally. The authors suggest it is a type I or immunoglobulin E–mediated allergic reaction because of the rapid occurrence and development of urticaria. Haeney[2] reported on a patient who repeatedly developed angioedema and urticaria two hours after ingestion of omeprazole 20-mg capsules but not after use of enteric-coated granules without the capsule shell (which in Europe consists of gelatin, red iron dioxide, and titanium dioxide), suggesting a causal relationship with the capsule shell and not with omeprazole. The triggering constituent was not identified. Bowlby and Dickens[3] reported on a patient who developed angioedema and urticaria immediately after taking oral omeprazole 20 mg, which was confirmed by rechallenge. Challenge with omeprazole granules without the capsule shell was also positive, which suggests an allergy to the drug and not to the capsule. Galindo et al.[4] reported on a patient who developed anaphylaxis a few minutes after infusion of omeprazole 40 mg; evidence of cross-reactivity was provided by skin tests to omeprazole and lansoprazole. As shown in Table 1, the Uppsala Monitoring Centre (UMC) of the World Health Organization (WHO) has received case reports of anaphylactic reactions (WHO Adverse Reaction Terminology preferred the terms anaphylactic shock and anaphylactoid reaction) in suspected connection with the PPIs lansoprazole (n = 12), omeprazole (n = 27), and pantoprazole (n = 3) (case reports with more than one suspected drug included). The UMC database contains summaries of case reports of suspected adverse drug reactions that are heterogeneous in regard to the quality of their documentation and causality assessment.

As a comparison, numbers are given of the anaphylactic reactions reported in association with the histamine$_2$-blockers cimetidine and ranitidine, and of the total number of anaphylactic reactions to drugs reported in the UMC database. The reporting rates in the UMC database suggest that the frequency of anaphylactic reactions, including anaphylactic shock to PPIs, is comparatively low.

The available evidence indicates that the PPIs currently in use can cause anaphylactic reactions. These benzimidazole derivatives are chemically related; observations in a few patients suggest that cross-sensitivity may occur. However, further study is needed to provide more precise information regarding the frequency of anaphylactic reactions during the use of these drugs. Because anaphylaxis is a potentially serious reaction, healthcare professionals need to be aware when prescribing these agents that PPIs can occasionally cause anaphylactic reactions.

Table 1. Reports of Anaphylactic Reactions in the UMC Database (May 1999)

Drug	Anaphylactic Reactions[a] (no. reports)[b,c]	All Adverse Reactions (total no.)	Anaphylactic Reactions (% of all reported adverse reactions)
Lansoprazole	12	4745	0.2
Omeprazole	27	17 258	0.2
Pantoprazole	3[d]	849	0.4
All PPIs	42	22 739	0.2
Cimetidine	97	22 781	0.4
Ranitidine	150	22 827	0.7
All drugs	28 112	3 437 751	0.8

PPIs = proton-pump inhibitors; UMC = Uppsala Monitoring Centre; WHOART = World Health Organization Adverse Reaction Terminology.
[a]WHOART preferred the terms anaphylactic shock and anaphylactoid reaction.
[b]Reports with more than one suspected drug included.
[c]All routes; mostly oral administration.
[d]Including one case with amoxicillin as simultaneously suspected drug.

Summary

The two patients described here experienced anaphylactic reactions, probably induced by PPIs. One patient had reactions to omeprazole and lansoprazole, respectively, suggesting cross-allergy. The other patient had anaphylactic shock after taking pantoprazole, an adverse reaction not previously described in the published literature. As of May 1999, the UMC has received a total of 42 reports of anaphylactic reactions or anaphylactic shock in association with PPIs (lansoprazole 12, omeprazole 27, pantoprazole 3). These reports account for 0.2% of the total of reported suspected adverse drug reactions to PPIs, compared with 0.8% anaphylactic reactions in the UMC database as a whole. These findings suggest that the PPIs can, a group, cause anaphylactic reactions and that the frequency is comparatively low.

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EXTRACTO

OBJETIVO: Informar dos casos de reacciones anafilácticas secundarias al uso de inhibidores de la bomba de protones.

RESUMEN DE LOS CASOS: Una mujer de 54 años es tratada con omeprazole y luego de 45 minutos de tomar una cápsula de 40 mg, desarrolla edema periorbital, edema de la piel, prurito, nausea, y vómitos. La paciente había sido expuesto previamente a omeprazole. Cinco meses más tarde, la paciente fue tratada con lansoprazole 30 mg. Nuevamente en los primeros 45 minutos, desarrolló una reacción más severa con prurito y urticaria en todo el cuerpo, sudoración, edema facial, y pérdida de conocimiento. El segundo caso es de un hombre de 61 años que fue tratado con pantoprazole 40 mg. Un año más tarde, tomó una tableta de pantoprazole 40 mg. En horas luego de la ingestión, el paciente desarrolló malestar, prurito generalizado, y urticaria inflamación de la lengua y los ojos y sudoración difusa. La presión sanguinea disminuyó a 75/50 mm Hg.

DISCUSIÓN: Debido a la presentación aguda de los síntomas en estos dos pacientes, se estableció una asociación temporal cercana a la ingesta del medicamento asi como también al hecho de que ambos habían recibido el medicamento previamente. Las reacciones podrían clasificarse como un choque anafiláctico a los inhibidores de la bomba de protones. Estos derivados de benzimedazoles se relacionan químicamente y se ha observado en algunos pacientes como el descrito en el primer caso que puede ocurrir sensitividad cruzada. El Centro de Monitoreo Uppsala ha recibido un total de 42 reportes de casos de reacciones anafilácticas asociadas al uso de inhibidores de la bomba de protones. Estos casos reportados representan el 0.2% de todas las reacciones adversas a los inhibidores de la bomba de protones y 0.8% del total de reacciones anafilácticas reportadas a este centro.

CONCLUSIONES: Estos hallazgos sugieren que los inhibidores de la bomba de protones pueden causar reacciones anafilácticas. Sin embargo, la frecuencia de esta reacción es baja. Las reacciones anafilácticas son reacciones potencialmente peligrosas y por lo que es necesario obtener información precisa en relación a su frecuencia. Los profesionales de la salud deben conocer la posibilidad de que ocurra este tipo de reacción al prescribir estos agentes.

ANNETTE PÉREZ

RÉSUMÉ

OBJECTIF: Rapporter deux cas de réactions anaphylactiques associées à l'utilisation d'inhibiteurs de la pompe à protons (IPP).

RÉSUMÉ DES CAS: Une femme de 54 ans était traitée avec de l'oméprazole 40 mg et a présenté un œdème péri-orbitaire, de l'œdème cutané, du prurit, des nausées, et des vomissements environ 45 minutes après avoir pris le médicament. Elle avait déjà utilisé l'oméprazole dans le passé. Cinq mois plus tard, elle reçut du lansoprazole 30 mg. Dans les 45 minutes qui suivirent la prise du médicament, elle présenta à nouveau une réaction, cette fois plus grave, avec prurit et urticaire affectant tout le corps, sudation, œdème facial, et perte de conscience. Un homme de 61 ans a pris un comprimé de pantoprazole 40 mg un an après avoir utilisé un premier traitement de pantoprazole. Dans les heures qui ont suivi la prise du médicament, le patient a présenté une sensation de malaise, du prurit et de l'urticaire généralisés, un œdème de la langue et des yeux et de la sudation. La pression sanguine a également diminué à 75/50 mm Hg.

DISCUSSION: Compte tenu de l'apparition rapide des symptômes, de l'association temporelle étroite existant entre l'exposition et la réaction au médicament ainsi que de la notion d'exposition antérieure à celui-ci, ces réactions peuvent être définies comme étant un choc anaphylactique aux IPP. Ces dérivés benzimidazoles sont chimiquement apparentés et les observations faites chez quelques patients, comme pour le premier cas rapporté ci-haut, suggèrent qu'une sensibilité croisée peut survenir. Le centre de surveillance d'Uppsala (CSU) a reçu un total de 42 rapports de cas de réactions anaphylactiques ou de chocs anaphylactiques associés à l'utilisation d'IPP. Ces rapports comptent pour 0.2% des réactions indésirables rapportées suite à la prise d'IPP comparativement à 0.8% de l'ensemble des réactions anaphylactiques inscrites dans la banque de données du CSU.

CONCLUSIONS: Ces données suggèrent que les IPP peuvent être à l'origine de réactions anaphylactiques. Cependant, l'incidence est faible. Puisque l'anaphylaxie est une réaction potentiellement grave, de l'information plus complète est nécessaire, notamment en ce qui a trait à sa fréquence. Les professionnels de la santé doivent être conscients de ce risque lorsqu'ils prescrivent ces médicaments.

ALAIN MARCOTTE