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## Hypersensitivity to Bismuth Subcitrate

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Almost half of the world's population is infected by *Helicobacter pylori*, with significant differences between geographical areas [1]. Approximately 80% of individuals with *H pylori* infection remain asymptomatic, although all infected individuals develop gastritis, which is associated with unpredictable and potentially serious outcomes, as well as with high morbidity and mortality [2,3]. This infection causes chronic gastritis, peptic ulcer, gastric mucosa-associated lymphoid tissue lymphoma, and gastric adenocarcinoma. It therefore requires curative treatment if clinical symptoms or complications are present or preventive treatment if there is a risk of complications, even in asymptomatic patients.

Empirically prescribed eradication therapy is considered acceptable if it reliably achieves, or preferably exceeds, cure rates of 90%. This goal is currently achieved in first- and second-line therapy only in quadruple regimens (with or without bismuth), which typically last 14 days. Recommended first-line approaches comprise a non-bismuth-based quadruple regimen (proton pump inhibitor, clarithromycin, amoxicillin, and metronidazole) and a bismuth-based quadruple regimen (proton pump inhibitor, bismuth, tetracycline, and metronidazole) [4]. Adherence can be improved by prescribing drugs such as Pylera, which contains a combination of bismuth subcitrate potassium (140 mg), metronidazole (125 mg), and tetracycline (125 mg).

We present the case of a 38-year-old woman with no personal history of atopy or allergy who was referred to our department after experiencing an immediate reaction consisting of right facial angioedema and conjunctival pruritus 10 minutes after taking the second dose of 3 capsules of Pylera. The symptoms resolved after administration of antihistamines and parenteral corticosteroids in the emergency department.

Prior to undergoing the drug allergy study, the patient was informed about the study, queries were addressed, and the informed consent form was signed.

We performed skin tests with Pylera (prick by prick), bismuth subcitrate (prick by prick), metronidazole (prick test [5 mg/mL] and intradermal test [1 mg/mL]), and tetracycline hydrochloride (prick test [125 mg/mL]), all of which were negative. We could not perform an intradermal test with tetracycline hydrochloride or bismuth subcitrate because

the parenteral preparation is not available in Spain. We then performed a drug provocation test (DPT) with 1 capsule of Pylera. The patient did not develop an immediate reaction in hospital but experienced a reaction at home 10 minutes after taking 3 capsules (right facial angioedema and ocular pruritus). Her condition improved within 2 hours of taking oral antihistamines. Individual DPTs were therefore performed for each component. No adverse reactions were observed for metronidazole (2 doses of 500 mg, the first administered in hospital and the second administered at home 12 hours later) and tetracycline hydrochloride (2 doses of 375 mg, administration as for metronidazole). However, the final DPT for bismuth subcitrate resulted in a positive reaction (2 doses of 360 mg, administration as in the previous tests), with the same symptoms as those triggered by Pylera (right facial angioedema and ocular pruritus 10 minutes after the second dose). The reaction resolved completely within 2 hours after administration of an antihistamine.

Despite the immediate onset of reaction and given the impossibility of performing an intradermal test, we performed a patch test with bismuth subcitrate diluted in 20% petrolatum and 20% water [5] in order to identify the causative mechanism. The result of the patch test was negative.

Hypersensitivity reactions to Pylera have been described, although they are rarely attributed to bismuth. Our review of the literature revealed 2 cases of hypersensitivity to bismuth. One was a case of bismuth-induced fixed drug eruption confirmed by a provocation test [6] and the other was a maculopapular eruption due to delayed-type hypersensitivity to bismuth salts [5]. Patch testing in the latter yielded positive results for Pylera and bismuth subcitrate and negative results for metronidazole and tetracycline. In Spain, the only bismuth salt currently marketed is bismuth subcitrate, which is present in 2 drugs (Gastrodenol and Pylera). In conclusion, we present a case of hypersensitivity to bismuth subcitrate in which skin tests were not helpful in the diagnosis, necessitating DPT to identify the offending drug.

We were therefore unable to determine the underlying immunological mechanism of the reaction. Clinicians should be aware of the possibility of a hypersensitivity reaction to bismuth, as this drug is increasingly used to treat *H pylori* infection.

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#### Conflicts of Interest

The authors declare that they have no conflicts of interest.

#### Previous Presentations

This case report was reported in electronic poster format at EAACI 2024.

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