

Hypersensitivity reactions associated with fidaxomicin use**Iarikov DE, Alexander J, Nambiar S**

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Summary: We report hypersensitivity reactions associated with fidaxomicin, an antibacterial drug approved for the treatment of *Clostridium difficile*-associated diarrhea (CDAD). These reactions are viewed as significant because of severity and unexpected because fidaxomicin is minimally absorbed.

Abstract

We report hypersensitivity reactions associated with fidaxomicin, an antibacterial drug approved for the treatment of *Clostridium difficile*-associated diarrhea (CDAD). These reactions are viewed as significant because of severity and unexpected because fidaxomicin is minimally absorbed. The fidaxomicin labeling was revised to include information about the possibility of hypersensitivity reactions.

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Fidaxomicin (DIFICID) is a macrolide antibacterial drug that was approved in the US for the treatment of *Clostridium difficile*-associated diarrhea (CDAD) in May 2011. The approved dosing regimen for fidaxomicin tablets is 200 mg taken orally twice daily. Fidaxomicin has a larger macrolide ring as compared to other macrolides. Fidaxomicin has an 18-membered carbon ring whereas other drugs in this group have 14-, 15-, or 16-membered rings. The main route of fidaxomicin metabolism is conversion to the primary metabolite OP-1118. The drug is minimally absorbed; maximal plasma concentrations of fidaxomicin and OP-1118 are in the ng/mL range [1].

While no specific concerns related to hypersensitivity reactions were identified during the drug development hypersensitivity reactions associated with fidaxomicin use have been reported to the FDA in the post-marketing period. After receiving these reports, we conducted a review of the FDA Adverse Event Reporting System (FAERS) and the literature.

We identified 12 cases; 11 cases were spontaneous reports and 1 case was reported in the literature [2]. The cases are summarized in Table 1. A history of macrolide allergy was reported in three out of 12 cases. No concomitant medications were listed in the reports for 8 cases. Review of the concomitant medications in 4 cases implicated fidaxomicin as the most probable explanation for hypersensitivity reactions.

Among the 12 cases of fidaxomicin hypersensitivity evaluated, 6 cases reported facial, tongue or throat swelling, 4 cases reported a diffuse rash, 1 case reported a burning

sensation in the throat, and the case from the literature had a purpuric rash on the lower extremities. The time to onset after first receiving fidaxomicin to a hypersensitivity event ranged from 1 hour to 7 days. Hypersensitivity reactions resolved in 10 cases – 9 events resolved after discontinuation of fidaxomicin and another event also resolved but the report did not clearly indicate whether fidaxomicin was stopped. In one case where fidaxomicin was continued along with diphenhydramine (Benadryl) rash and itching persisted. The outcome was unknown in one case.

Two cases reported a positive rechallenge to fidaxomicin. In the first rechallenge case, the patient developed tongue and facial swelling and dyspnea on the 5th day of fidaxomicin treatment approximately 9 hours after fidaxomicin intake. The symptoms resolved after administration of antihistamines and intravenous hydrocortisone. When the patient restarted fidaxomicin the next day, he experienced facial and tongue swelling shortly after taking the drug. In the second rechallenge case, the patient developed swelling of the throat that resolved after the discontinuation of fidaxomicin. The patient experienced a similar reaction when she was retreated with fidaxomicin for recurrent CDAD one month later.

A literature report described a 79- year-old man who developed purpuric rash on the lower extremities on day 7 of fidaxomicin administration. A skin biopsy of this patient's rash was consistent with a delayed type 4 hypersensitivity reaction.

Based on the information described above, the Contraindications, Warnings and Precautions, and Adverse Reactions sections of the fidaxomicin labeling were revised in March 2013 [1]. Known hypersensitivity to fidaxomicin is listed as a contraindication for fidaxomicin use. The Warnings and Precautions section provides information about acute hypersensitivity reactions, including dyspnea and angioedema that may be associated with fidaxomicin. The warning also indicates that a history of macrolide allergy should be taken into consideration when prescribing fidaxomicin given that 3 of the 12 cases reported a history of previous macrolide allergy.

Interestingly, allergic reactions including anaphylaxis after administration of oral vancomycin, another minimally absorbed drug, in the treatment of CDAD have been reported [3, 4]. It has been suggested that colonic inflammation in the case of *C. difficile* infection can significantly increase the bioavailability of the drug. It has been also hypothesized that in a predisposed patient a minimal systemic exposure or even contact with inflamed mucosa could be sufficient to cause an allergic reaction.

In conclusion, the described events are consistent with hypersensitivity reactions associated with fidaxomicin use. The two cases of positive rechallenge support this association. As fidaxomicin is minimally absorbed, such adverse reactions are not expected and may not be considered especially in a patient with multiple concomitant medications. Healthcare providers should be aware of the risk of hypersensitivity reactions with fidaxomicin. It is also important that these adverse reactions be reported to the FDA MedWatch program (<http://www.fda.gov/Safety/MedWatch>).

Note: The authors have no reported conflicts of interest.

Reference List

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Table 1: Summary of cases of hypersensitivity to fidaxomicin						
#	Age /Sex	Day of treatment	Time to reaction after the last dose	Time to resolution	Reaction description	Actions <i>History of macrolide allergy</i>
1	73M	5	45 min	24 hours	Diffuse rash	Fidaxomicin was discontinued
2	74 F	After the 1 st dose	1-2 hours	2 days	Rash, swollen lips and eyes	Whether fidaxomicin was discontinued is unknown; Benadryl prescribed
3	26 F	5	Unknown	24 hours	Diffuse rash	Fidaxomicin was discontinued
4	49 F	After the 1 st dose	1 hour	Unresolved	Diffuse rash and itching	Fidaxomicin was continued along with Benadryl <i>Erythromycin/Azithromycin allergy</i>
5	79 F	After 2 doses	Unknown	Resolved, time unknown	Burning sensation in the throat; no difficulty with swallowing or breathing	Fidaxomicin discontinued <i>Erythromycin allergy</i>
6	UNK F	2 - rechallenge in 1 month ^a	Unknown	Resolved, time unknown	Swelling of the throat and chest	Fidaxomicin was discontinued <i>Erythromycin allergy</i>
7	53 F	3	Unknown	Resolved, time unknown	Swelling of the eyelids, lips, and inside of mouth; itching of the face	Fidaxomicin was continued along with Benadryl
8	56 M	5	8.45 hours	Resolved	Angioedema of the tongue, face and neck, accompanied by dyspnea	Fidaxomicin was interrupted; Steroids and antihistamines administered
		6 - rechallenge ^b	1-2 hours	Dyspnea resolved; neck edema persisted for several days, but finally resolved	Angioedema of the tongue, face and neck, accompanied by dyspnea	Fidaxomicin was discontinued; Steroids and antihistamines administered
9	UNK F	7 days	Unknown	Unknown	Lip swelling	Fidaxomicin was discontinued
10	UNK M	Unknown	Unknown	Resolved	Severe rash	Fidaxomicin was discontinued Unspecified treatment was provided for rash
11	50 F	2 (after two of three doses)	10 min	Resolved within one hour	Shortness of breath, tightness in the chest, and swelling in the throat	Fidaxomicin was discontinued Benadryl, EpiPen (epinephrine injection), and prednisone given

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12	79 M (2)	5	Unknown	Improved within 72 hours, resolved within 3 weeks	On day 5 - bilateral lower extremity edema On day 7 - a nonblanching, nonpruritic, nonpalpable, ecchymotic purpuric rash on the lower extremities;	Fidaxomicin was discontinued Patient tolerated macrolide in the past
^a Similar reaction when treated for CDI recurrence in a month after the initial episode						
^b Similar reaction after 2 more doses of fidaxomicin were given the next day						