FEATURED ARTICLE

Acute Generalized Exanthematous Pustulosis in Association with Hydroxyzine and Cetirizine

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ABSTRACT

Purpose: To review the occurrence of acute generalized exanthematous pustulosis (AGEP) with exposure to hydroxyzine and its active metabolites, cetirizine, and levocetirizine.

Methods: The Division of Pharmacovigilance of the Food and Drug Administration (FDA) searched the FDA Adverse Event Reporting System (FAERS) and the medical literature for cases of AGEP reported in association with use of hydroxyzine, cetirizine, and levocetirizine. Causality was assessed using a modified World Health Organization Uppsala Monitoring Centre (WHO-UMC) causality assessment tool.

Results: The FDA identified 26 cases of AGEP reported in association with the use of hydroxyzine (n = 21), cetirizine (n = 5), and levocetirizine (n = 3) (three cases included more than one drug product). Hydroxyzine causality was probable in five of the cases, and cetirizine causality was probable in two of the cases. All levocetirizine cases were assessed as unlikely.

Conclusions: Our findings supported an association between hydroxyzine and cetirizine and AGEP. As a result, FDA has required labeling changes for hydroxyzine products to inform clinicians to avoid using hydroxyzine, cetirizine, and levocetirizine in patients who have experienced AGEP or other hypersensitivity reactions to any one of the above agents due to the risk of cross-reactivity.

INTRODUCTION

Acute generalized exanthematous pustulosis (AGEP) is an acute febrile cutaneous eruption, characterized by numerous small, superficial, non-follicular sterile pustules, arising within large areas of edematous erythema. More than 90% of cases of AGEP are drug induced.[1] It is serious, though typically not life-threatening once the offending drug is identified and discontinued. If drug exposure persists, the clinical picture may evolve into a toxic epidermal necrolysis (TEN)-like picture with the complications of TEN (e.g., fluid loss, bacterial infections). Hydroxyzine is an antihistamine approved in the United States for symptomatic relief of anxiety, management of allergic pruritus, and as a sedative when used as a premedication and following general anesthesia. Hydroxyzine's active metabolites, cetirizine and levocetirizine, are marketed as antihistamines in the United States. In this report, we describe our review of the occurrence of AGEP with hydroxyzine, cetirizine, and levocetirizine.

Methods

The Division of Pharmacovigilance of the Food and Drug Administration (FDA) searched the FDA Adverse Event Reporting System (FAERS) and the medical literature for cases of AGEP reported in association with use of hydroxyzine, cetirizine, and levocetirizine. The FAERS database supports FDA's post-marketing safety surveillance program for drugs and therapeutic biologics.[a] It contains adverse event and medication error reports submitted to the FDA from product manufacturers, consumers, and healthcare professionals. Using a modified World Health Organization Uppsala Monitoring Centre (WHO-UMC) causality assessment tool[b], causality was assessed as probable, possible, or unlikely based on the documented diagnosis of AGEP (as confirmed by histology or diagnosed by a dermatologist), time relationship to drug intake, response to drug withdrawal, and whether AGEP could be attributed to an underlying disease or other drugs.

Results

The FDA identified 26 cases of AGEP reported in association with the use of hydroxyzine, cetirizine, and levocetirizine. Six cases originated from the medical literature – five involving hydroxyzine and one involving cetirizine.[2-7] Twenty-two of the 26 cases required hospitalization as a result of AGEP. In all 26 cases, patients recovered from AGEP after discontinuing the drug ("positive dechallenge"). In three cases, reoccurrence of AGEP was reported after re-exposure to the drug ("positive rechallenge"), all involving hydroxyzine. Table 1 provides additional characteristics of the 26 cases. Table 2 provides a summary of the causality assessment.

[a] For additional information on FAERS: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm

[b] For additional information on the WHO-UMC causality assessment tool: http://www.who-umc.org/media/2768/standardised-case-causality-assessment.pdf

Table 1. Selected characteristics of acute generalized exanthematous pustulosis cases reported in association with hydroxyzine, cetirizine, and levocetirizine received by the FDA through March 30, 2016 (n=26)

Age, years	Mean = 52.1
	Median = 57.5
	Range = 11 to 93
Sex	Female = 14
	Male = 12
Time to onset of AGEP from initiation of drug product of interest, days (n = 25)	Mean = 3.2
	Median = 1
	Range = 0 to 13
No. (%) Drug product reported*	Hydroxyzine only = 19 (73)
	Cetirizine only = 3 (12)
	Levocetirizine only = 1 (4)
	Hydroxyzine + cetirizine* = 1 (4)
	Cetirizine + levocetirizine* = 1 (4)
	Hydroxyzine + levocetirizine* = 1 (4)
*** Three cases reported more than one drug product of interest as a suspect or concomitant drug.**	
AGEP = Acute generalized exanthematous pustulosis.	

Table 2. Causality assessment for acute generalized exanthematous pustulosis cases reported with hydroxyzine, cetirizine, and levocetirizine, received by the FDA through March 30, 2016 (n=26)

Drug Product	Probable	Possible	Unlikely
No. (%) Hydroxyzine (n=21*)	5 (24)	8 (38)	8 (38)
No. (%) Cetirizine (n=5*)	2 (40)	2 (40)	1 (20)
No. (%) Levocetirizine (n=3*)	0	0	3 (100)
*** Causality assessment was performed for each drug product reported in a case. Three cases reported more than one drug product of interest per case, so the sum of causality assessments for individual drug products equals more than the total number of cases in the case series (29 vs. 26).**			

Discussion

Our findings support an association between hydroxyzine and cetirizine and AGEP. All cases reported a close temporal relationship (Median 1 day after drug initiation), and positive dechallenges. Three cases reported a positive rechallenge. We did not find evidence of a plausible association between levocetirizine and AGEP. Hydroxyzine has been marketed since 1956, and cetirizine is a widely used antihistamine, so AGEP may be a rare adverse reaction to these drugs. However, a contributing factor to the few reports received by FDA may include overlooking the diagnosis, as hydroxyzine and cetirizine are often used to treat allergic skin conditions, and a worsening of the rash may be attributed to the underlying condition. Based on the data in this analysis, the prescribing information of hydroxyzine was revised with a precaution about the rare, but serious, consequences of AGEP, and instructs clinicians to discontinue treatment with hydroxyzine if patients develop signs or symptoms of AGEP. Clinicians should avoid using hydroxyzine, cetirizine, and levocetirizine in patients who have experienced AGEP or other hypersensitivity reactions to any one of the above agents due to the risk of cross-reactivity. Cetirizine is currently regulated as an over-the-counter (OTC) product only, and the cetirizine OTC Drug Facts label was deemed to contain sufficient allergy warnings. The levocetirizine prescribing information was updated with the addition of postmarketing reports of AGEP with cetirizine.[c]

[c] For complete prescribing information: https://dailymed.nlm.nih.gov/dailymed/

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