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Eszopiclone-Induced Drug Eruption: A Case Report

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Abstract

Eszopiclone is a non-benzodiazepine hypnotic widely used for the treatment of insomnia. Although non-cutaneous adverse effects are well recognized, cutaneous drug reactions associated with eszopiclone have not previously been reported. A 49-year-old Japanese man developed multiple asymptomatic scaly erythematous papules and plaques on the trunk and upper extremities approximately two months after initiation of eszopiclone, escitalopram, and ethyl loflazepate. The eruption persisted despite replacement of escitalopram and ethyl loflazepate. Histopathological examination revealed focal parakeratosis, mild spongiosis, basal vacuolar degeneration, and superficial perivascular lymphocytic infiltration with scattered eosinophils. A lymphocyte stimulation test showed a stimulation index of 2.0 for eszopiclone, whereas those for sertraline and diazepam were below the institutional diagnostic threshold. The eruption resolved almost completely within two months after discontinuation of eszopiclone and treatment with topical corticosteroids, without recurrence. Clinicians should consider eszopiclone as a potential causative drug in patients presenting with cutaneous eruptions while receiving multiple psychotropic medications.

Categories: Dermatology
Keywords: case report, drug eruption, eszopiclone, gaba-a, lymphocyte stimulation test

Introduction

Eszopiclone is a cyclopyrrolone-derived non-benzodiazepine hypnotic widely prescribed for the treatment of insomnia that selectively binds to the benzodiazepine-binding site of the γ-aminobutyric acid type A (GABA-A) receptor [1,2]. Although non-cutaneous adverse effects of eszopiclone, including dysgeusia and somnolence, are well recognized [3], cutaneous drug reactions associated with eszopiclone appear to be extremely rare. Herein, we describe a case of papulosquamous drug eruption associated with eszopiclone administration.

Case Presentation

A 49-year-old Japanese male was referred to our department with a two-month history of multiple scaly erythematous papules and plaques on the trunk and both upper extremities. He had been treated for depression for approximately one year. Four months before presentation, eszopiclone, escitalopram, and ethyl loflazepate had been initiated for insomnia and depressive symptoms. Approximately two months later, asymptomatic papules gradually developed on the forearms and trunk. Escitalopram and ethyl loflazepate were replaced with sertraline and diazepam because a drug eruption was suspected; however, the skin lesions persisted, and he was referred to our department.

Physical examination revealed symmetrically distributed, discrete erythematous papules measuring 3-8 mm in diameter with fine adherent scales on the trunk and upper extremities (Figure *1A*). The lesions were relatively monomorphic without vesiculation, ulceration, or mucosal involvement. No lymphadenopathy or systemic symptoms were observed. Fungal examination was negative, and the patient had no prodromal symptoms suggestive of a viral infection, such as fever or upper respiratory symptoms.

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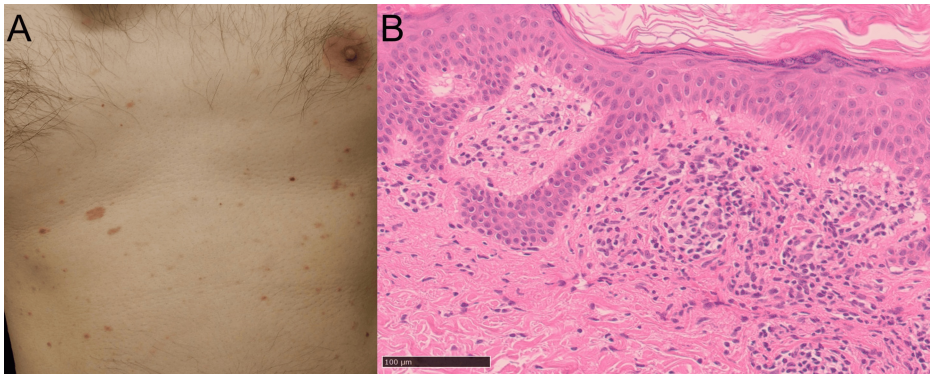


FIGURE 1: Clinical and histopathological findings.

(A) Multiple symmetrically distributed erythematous papules with fine adherent scales on the trunk. (B) Histopathological examination demonstrated focal parakeratosis, mild spongiosis, scattered necrotic keratinocytes, vacuolar degeneration of the basal layer, and superficial perivascular lymphocytic infiltration with scattered eosinophils (hematoxylin-eosin stain, original magnification ×100).

A skin biopsy examination taken from the erythematous plaque demonstrated focal parakeratosis, mild spongiosis, vacuolar degeneration of the basal layer, and superficial perivascular lymphocytic infiltration with scattered eosinophils (Figure *1B*). In addition, immunohistochemical staining for CD3, CD4, and CD8 was not performed, limiting the detailed characterization of T-cell infiltration in the skin lesions. A lymphocyte stimulation test (LST) was performed for the suspected medications, and the stimulation index (SI) was 2.0 for eszopiclone, whereas the SI values for sertraline and diazepam were both 1.5, below the institutional diagnostic threshold. Taken together, the temporal relationship, clinicopathological findings, and selective LST positivity supported the diagnosis of an eszopiclone-induced drug eruption. The eruption resolved almost completely within two months after discontinuation of eszopiclone and treatment with topical corticosteroids, without recurrence. Clinicians should consider eszopiclone as a potential causative drug in patients presenting with cutaneous eruptions while receiving multiple psychotropic medications.

Discussion

Cutaneous adverse reactions to eszopiclone appear to be exceptionally rare despite its widespread clinical use. In contrast, several cutaneous adverse reactions have been reported with benzodiazepine derivatives [4,5]. This difference is intriguing because both benzodiazepines and eszopiclone exert their pharmacological effects through the benzodiazepine-binding site of the GABA-A receptor.

Although cutaneous adverse events, including rash and dermatitis, have been reported in clinical trials of eszopiclone, detailed case reports with clinicopathological evaluation remain scarce. To our knowledge, no previously published case report has described a papulosquamous drug eruption associated with eszopiclone supported by histopathological findings and an LST. Diazepam has been shown to inhibit T-cell proliferation and cytokine production in vitro [6], whereas other benzodiazepines have exhibited quantitatively or qualitatively different effects on lymphocyte responses [7]. Thus, GABA-A receptor activity alone is unlikely to determine the occurrence of drug hypersensitivity. Drug-specific factors, including molecular structure, metabolism, formation of antigenic metabolites, and receptor pharmacology, may also contribute to differences in hypersensitivity risk among benzodiazepine and non-benzodiazepine hypnotics. However, the relevance of these factors to eszopiclone-induced drug eruption remains unknown.

GABA-A receptors are expressed on immune cells, including T lymphocytes, and experimental studies have shown that GABA-A receptor signaling can modulate T-cell proliferation and cytokine production [8]. However, these observations have largely been obtained using GABA or experimental GABAergic modulation and cannot be directly extrapolated to eszopiclone at therapeutic exposure. In a pharmacokinetic study in healthy adults, the mean plasma Cmax of eszopiclone following a single 3-mg dose was approximately 38 ng/mL [9]. There is currently no direct clinical evidence that eszopiclone at therapeutic concentrations suppresses T-cell responses or allergic skin inflammation. Therefore, any contribution of GABA-A receptor-mediated immunomodulation to eszopiclone-associated drug hypersensitivity remains speculative and requires validation under clinically relevant exposure conditions. Interestingly, cutaneous adverse events associated with nemolizumab, an interleukin-31 (IL-31) receptor antagonist, have been proposed to involve alterations in T-cell responses and cytokine balance [10]. These observations suggest that pharmacological modulation of immune signaling may be accompanied by unexpected cutaneous inflammatory reactions. However, the mechanisms underlying nemolizumab-associated adverse events differ from those potentially involved in eszopiclone-associated drug eruptions, and no direct mechanistic relationship has been established.

This report has several limitations. Although the LST yielded an SI of 2.0 for eszopiclone, LST has imperfect sensitivity and specificity, and both false-positive and false-negative results may occur. Moreover, values close to the diagnostic cutoff should be interpreted cautiously. Therefore, the LST result alone cannot definitively establish eszopiclone as the causative drug and should be interpreted together with the temporal relationship, clinical course, and clinicopathological findings. In addition, there is currently insufficient clinical evidence to determine whether GABA-A receptor-mediated immunomodulation at therapeutic concentrations of eszopiclone meaningfully affects either the occurrence of allergic drug reactions or the diagnostic performance of LST. Thus, the proposed immunological mechanism remains speculative. Further accumulation of cases and additional studies under clinically relevant exposure conditions are needed to clarify these issues.

Conclusions

In conclusion, the eruption resolved almost completely within two months after discontinuation of eszopiclone and treatment with topical corticosteroids, and no recurrence was observed. Although the underlying immunological mechanism remains unclear, clinicians should consider eszopiclone as a potential causative drug when evaluating cutaneous eruptions in patients receiving multiple psychotropic medications.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

Concept and design: Yu Sawada, Natsuko Saito-Sasaki, Manami Noda

Acquisition, analysis, or interpretation of data: Yu Sawada, Natsuko Saito-Sasaki, Manami Noda

Drafting of the manuscript: Yu Sawada, Natsuko Saito-Sasaki, Manami Noda

Critical review of the manuscript for important intellectual content: Yu Sawada, Natsuko Saito-Sasaki, Manami Noda

Disclosures

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