Adverse cutaneous drug reaction due to possible lorazepam in a 12-year-old patient with Hunter Syndrome

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SUMMARY

Benzodiazepines may cause adverse cutaneous reactions in about 0.3% of patients, with lorazepam linked to hypersensitivity and exanthematous eruptions in adults. Lorazepam, an intermediate-acting benzodiazepine, is commonly prescribed for anxiety and status epilepticus, and its pharmacological effects are mediated by gamma-aminobutyric acid (GABA). This report presents a lorazepam-induced skin reaction in a 12-year-old male patient with Hunter syndrome, which improved after discontinuation of lorazepam therapy.

Key words: Lorazepam, drug rash, Hunter syndrome, side effect

INTRODUCTION

Benzodiazepines are known to cause adverse cutaneous reactions in approximately 0.3% of the patient (1).Hypersensitivity reactions, anaphylactoid reactions, dermatological symptoms, and allergic skin reactions (rash, unspecified) have been reported during lorazepam therapy in adults (2). An exanthematous eruption is the most common type of reaction (1).

Lorazepam is an intermediate-acting benzodiazepine commonly used in treatment of anxiety, status epilepticus, and the short-term treatment of insomnia secondary to anxiety. Common off-label uses include chemotherapy-induced nausea/vomiting and agitation of various etiologies (3). The action of benzodiazepines is mediated through the inhibitory neurotransmitter gamma-aminobutyric acid. There are only a few reports on lorazepam-induced skin reactions in adults (4–6). We report a case of lorazepam-induced skin reaction in a 12-year-old patient with Hunter syndrome, and the improvement of the skin reaction following the discontinuation of lorazepam therapy.

CASE

A 12-year-old boy was admitted to the pediatric metabolism clinic with his father for an enzyme treatment. He was a known case of Hunter syndrome with severe intellectual disability, non-verbal, epilepsy, and hearing loss. He was receiving long-term treatment with risperidone 1 mg twice a day, levetiracetam 700 mg twice a day, and quetiapine 25 mg three times a day for behavioral problems and epilepsy. He was consulted to the child and adolescent psychiatry department by the pediatric metabolism disorders department with his symptoms of increased aggression to himself and others. It was determined that the patient was extremely active, yelling and screaming, had restlessness, and disturbed sleep (initial insomnia and fitful sleep with frequent nocturnal awakenings) complaints as a result of the history taken from the family and mental examination. It was learned that these symptoms have been present for the past two weeks, accompanied by aggressive behaviors such as hurling objects, harming others, and self-harm. There was no history of a similar episode before. Upon initial examination, it was observed that the patient was restrained by his wrists and ankles and had poor eye contact. He was uncooperative, with

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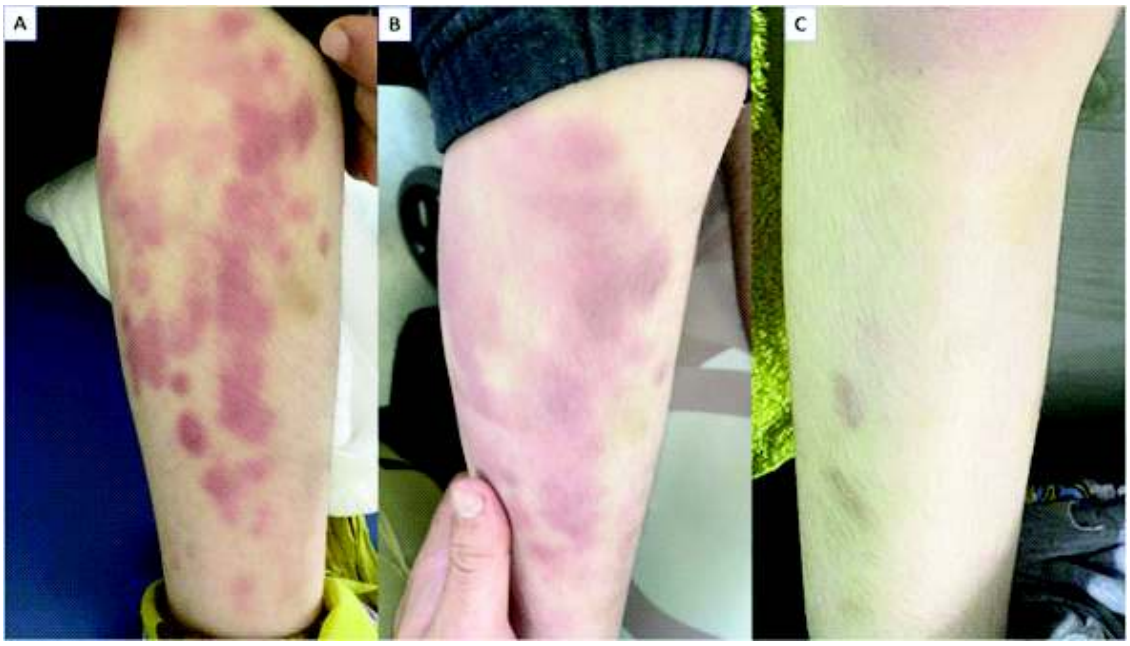

Figure 1: Photographs of the right leg of a 12-year-old boy with drug reactions due to lorazepam. (A) multipl erythematous and slightly papular macules after taking the first dose of lorazepam. (B) 24 hours after discontinuating lorazepam on the same region. (C) At follow-up one month later, most of the existing lesions improved with residual hyperpigmentation.

increased psychomotor activity. He was consulted to the child neurology department to exclude a possible underlying organic pathology, and no evidence of an organic pathology was found. Cranial computed tomography showed no new findings compared to previous examinations. Agitation due to acute psychotic or manic episodes was considered. Lorazepam oral tablet (2 mg daily in divided doses) was initiated for the rapid tranquilization of the patient with severe psychomotor agitation. About 8-10 hours after starting the lorazepam 1 mg, a physical examination revealed multiple erythematous and slightly papular macules (the largest is nearly 1 cm diameter) on the front and sides of the bilateral legs (Figure 1A). The other areas of skin, oral, and conjunctival mucosa were not affected. A comprehensive assessment, including vital signs, systemic examination, and laboratory workup, did not reveal any explanatory etiology for his symptoms. Drug reaction with eosinophilia and systemic symptoms syndrome and HHV-6 infection were excluded. Although the dermatology department recommended patch testing, it could not be performed due to the patient's failure to adhere to the testing procedure. The patient's lesions were considered secondary to lorazepam due to the temporal relation between the starting of the drug and the occurrence of lesions, and lorazepam was discontinued. Due to existing behavioral problems, risperidone was gradually increased to 3mg/day, and the quetiapine dose was continued at the same dose (75 mg/day). The day after discontinuing lorazepam, the existing lesion began to regress without any intervention (Figure 1B). His skin rash resolved within 10 days of discontinuation of lorazepam, and the patient was discharged.

At the first outpatient follow-up one month later, most of the existing lesions improved spontaneously without any intervention. However, the patient had residual hyperpigmented lesions in the involved site after resolution (Figure 1C). Besides lorazepam, he also regularly used risperidone, quetiapine, and levetiracetam, none of which seemed to induce any skin reactions. We obtained verbal and written consent from the family to publish this report and to include the patient's photograph.

DISCUSSION

Drug-induced skin reactions are classified into two types: Type A and Type B (7,8). Type A reactions

result from the pharmacological or toxic effects of the drug and are generally more common, dose-dependent, and predictable. Examples include anticholinergic and extrapyramidal side effects. In contrast, Type B reactions are idiosyncratic and unpredictable, arising from genetic or metabolic predispositions. These reactions are typically Type I and Type IV hypersensitivity responses and can occur independently of dosage. Type B reactions may be more severe and can affect multiple organ systems. Additionally, skin reactions can sometimes occur through non-immune-mediated mechanisms, such as accumulating toxic metabolites. These reactions are usually more predictable and dose-dependent, but the exact cause may not always be identified.

Lorazepam is often used for the short-term treatment of insomnia secondary to anxiety and status epilepticus in children and adolescents. Furthermore, there is evidence supporting the off-label use of lorazepam for the management of agitation in children and adolescents (9). The most commonly reported adverse effects include sedation, drowsiness, impaired concentration, and memory difficulties. Although allergic reactions to benzodiazepines are rare, delayed hypersensitivity reactions have been reported (4), including fixed drug eruption due to lormetazepam (5) and lorazepam (6) in adults. In children and adolescents, there is no case that linked adverse cutaneous reaction to lorazepam use.

In the present case, the adverse skin reaction is most likely a probable cutaneous adverse effect of lorazepam. Our patient's cutaneous findings, which were not evident before treatment, emerged after lorazepam use. Supporting a lorazepam-induced adverse cutaneous reaction, laboratory test results and systemic examination were normal, DRESS syndrome and HHV-6 were ruled out, and the lesion began to regress after stopping lorazepam. The Naranjo adverse drug reaction probability scale score in the present case was 8, indicating a probable side effect (10).

Hunter syndrome is a lysosomal storage disease that affects the breakdown of sugar in the body. Metabolic disturbances and impaired drug metabolism associated with systemic diseases, along with the accumulation of toxic metabolites in the body, may result in adverse cutaneous side effects. The mechanism through which lorazepam causes skin reactions is mainly unknown. In our case, it was considered that the skin reactions developing after the drug administration could be a hypersensitivity reaction; however, a patch test could not be performed to confirm the diagnosis.

Consequently, particular attention should be paid to potential cutaneous reactions during drug therapy, especially in pediatric patients with underlying metabolic conditions. In the present case, the resolution of the rash following the discontinuation of lorazepam underscores the importance of early intervention in the management of such reactions. Early detection of cutaneous reactions and the timely cessation of the offending drug are critical to preventing adverse outcomes in the patient's overall treatment course.

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