Generalized Bullous Fixed Drug Eruption Induced by Chlordiazepoxide: A Case Report of a Potentially Lethal Adverse Effect

Генерализованная буллезная фиксированная лекарственная эритема после применения хлордиазепоксида: клинический случай потенциально летального нежелательного явления

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Case report

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ABSTRACT

BACKGROUND: Fixed drug eruption is a type of adverse drug reaction affecting the skin, marked by recurrent rashes that appear at the same site each time a particular drug is taken. Generalized bullous fixed drug eruption (GBFDE) is a severe form of FDE characterized by vesicles or bullae and involvement of a significant portion of the body surface area. To date, no association between GBFDE and chlordiazepoxide has been reported in the literature.

CASE REPORT: The authors present the case of a 40-year-old male inpatient in the psychiatry department of a tertiary care hospital in Assam, India. The patient was admitted in an alcohol withdrawal state and was initially prescribed chlordiazepoxide at a dose of 60 mg/day. He developed GBFDE within a day of chlordiazepoxide administration. The drug was discontinued, and he was treated with oral and topical corticosteroids instead, resulting in a significant improvement.

CONCLUSION: Chlordiazepoxide is a rare but potential trigger of GBFDE. Clinicians should closely monitor patients on chlordiazepoxide for possible signs of GBFDE.

АННОТАЦИЯ

ВВЕДЕНИЕ: Фиксированная лекарственная эритема — это тип нежелательной лекарственной реакции, поражающей кожу и характеризующейся рецидивирующей сыпью, возникающей на одном и том же участке кожи при каждом применении определенного препарата. В случаях, когда фиксированная лекарственная эритема сопровождается везикулами или буллами и затрагивает значительную часть поверхности тела, она классифицируется как генерализованная буллезная фиксированная лекарственная эритема (ГБФЛЭ). На сегодняшний день в научной литературе отсутствуют сведения о связи между ГБФЛЭ и хлордиазепоксидом.

КЛИНИЧЕСКИЙ СЛУЧАЙ: Пациент, мужчина 40 лет, госпитализирован в психиатрическое отделение высокоспециализированной больницы в Ассаме, Индия. Пациент поступил в состоянии алкогольной абстиненции,

для лечения которой ему назначили хлордиазепоксид в таблетированной форме в дозе 60 мг/сут. В течение суток после начала приема хлордиазепоксида у пациента развилась ГБФЛЭ. Препарат отменили, а пациенту прописали пероральные и местные кортикостероиды, которые улучшили его самочувствие.

ЗАКЛЮЧЕНИЕ: Хлордиазепоксид является редким, но возможным триггером ГБФЛЭ. Важно сохранять высокий уровень клинической настороженности в отношении ГБФЛЭ у пациентов, принимающих хлордиазепоксид.

Keywords: *generalized bullous fixed drug eruption; chlordiazepoxide; alcohol withdrawal; benzodiazepines; adverse effect; case report*
Ключевые слова: *генерализованная буллезная фиксированная лекарственная эритема; хлордиазепоксид; алкогольная абстиненция; бензодиазепины; нежелательное явление; клинический случай*

INTRODUCTION

Fixed drug eruption (FDE) is a "distinct cutaneous drug eruption characterized by well-demarcated dusky-red or heavily pigmented patches involving the skin and mucosa. In recurrent episodes patients tend to develop lesions on the same location" [1]. The lesions commonly resolve with residual hyperpigmentation [1]. FDEs can be solitary, scattered, or generalized [2]. The generalized cases are sometimes associated with the eruption of bullae or erosions at multiple sites, a condition referred to as generalized bullous fixed drug eruption (GBFDE) [2]. GBFDE is the most severe form of FDE and can be misdiagnosed as epidermal necrolysis [3]. It has a high mortality rate of 22% [4]. Diagnosis of GBFDE requires "involvement of at least 10% of the body surface area (BSA) and at least three of six different anatomic sites (specifically, upper extremities, lower extremities, genitalia, the head and neck, anterior trunk, and back)" [5].

GBFDE secondary to chlordiazepoxide has never been reported in the literature, to the best of our knowledge. We present a case report of GBFDE following chlordiazepoxide administration in a 40-year-old male.

CASE REPORT

Patient information

General information

A 40-year-old married male, resident of Karnataka (India), educated up to 12th standard, employed in government service, of middle socio-economic status, with a history of alcohol consumption for the past 15 years, in a dependent pattern for the past 10 years, voluntarily admitted himself in the psychiatry ward on 8 Jul 2024 in an effort to quit alcohol.

The patient had no past history of allergy to drugs, or any medical, surgical, or psychiatric disorders.

Medical, family, and psycho-social history

The patient was born to a non-consanguineous couple. The father was a farmer with a history of regular consumption of alcohol and tobacco (however, a dependent pattern could not be established due to the lack of a detailed history). He passed away at the age of 59 years in 2019 following a road traffic accident. There is no history of any major medical/surgical illnesses in the family. No history of drug allergies in the family.

Clinical findings

A detailed history revealed features of alcohol dependence in the form of tolerance, craving, salience, and withdrawal discomfort upon abrupt cessation of alcohol consumption. Evaluation at the time of admission revealed moderate alcohol withdrawal state.

Diagnostic assessment

Diagnostic testing

The following scales were used to assess/grade the severity of alcohol use disorder:

1. Alcohol Use Disorders Identification Test [6]: patient scored 22, suggesting alcohol dependence.
2. Severity of Alcohol Dependence Questionnaire (SADQ-C) [7]: patient scored 34, suggesting severe alcohol dependence.
3. Alcohol withdrawal was assessed via Clinical Institute Withdrawal Assessment of Alcohol Scale, Revised (CIWA-Ar) [8]: patient scored 12, suggesting moderate withdrawal.

The patient's relevant hematological and biochemical investigations, including the blood counts, liver/renal functions, blood glucose, lipid/thyroid profiles, were within normal boundaries (it is worth noting that while abnormal

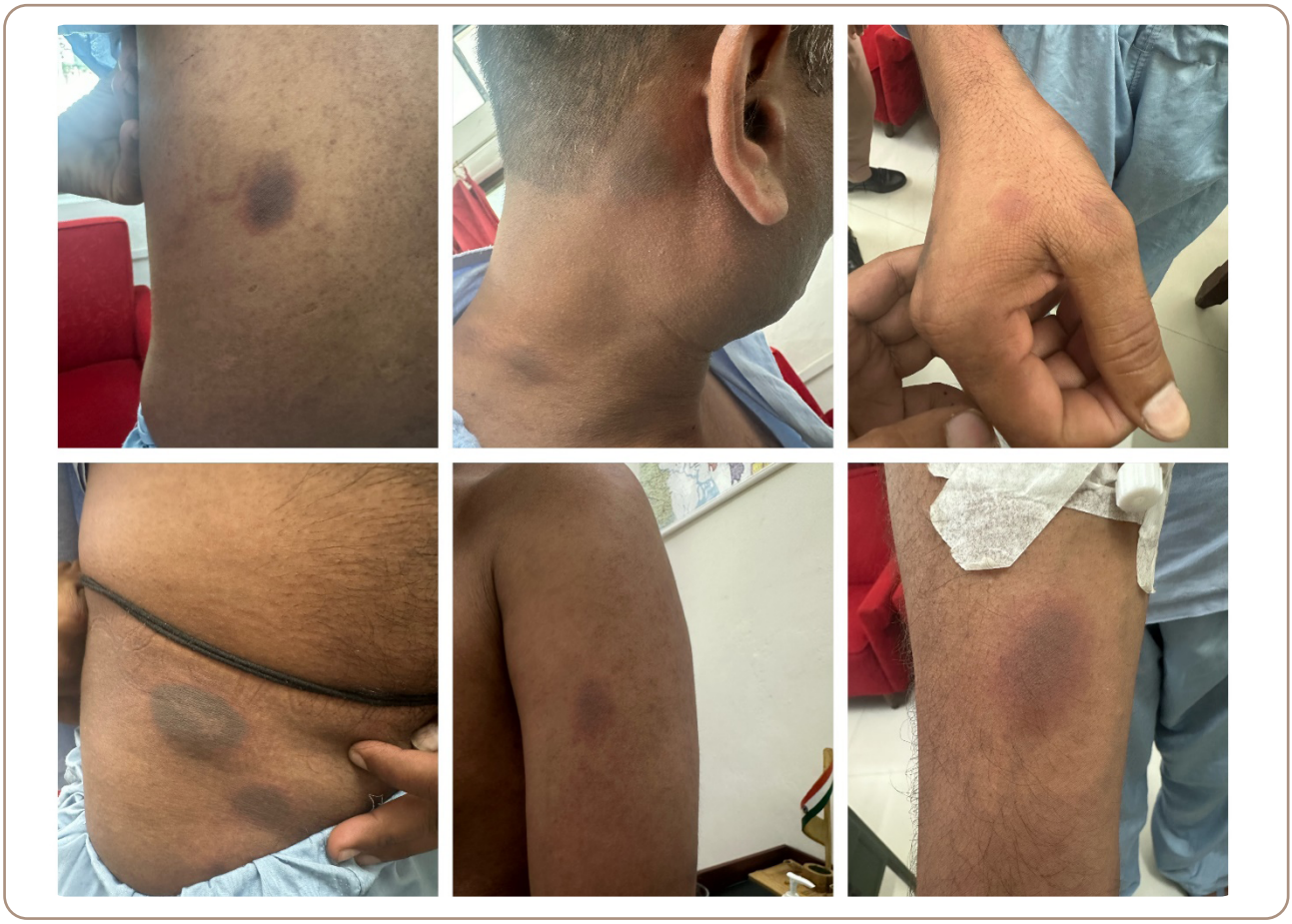

Figure 1. Resolving generalized bullous fixed drug eruptions involving multiple locations over the body following chlordiazepoxide administration.

Source: Singh R. et al, 2025.

liver functions are commonly observed in patients with long-term alcohol dependence, exceptions do occur, particularly in younger individuals with adequate nutritional status and no significant history of concurrent medical comorbidities).

Diagnosis

The patient was diagnosed as a case of:

1. Alcohol dependence syndrome, ADS (International Classification of Diseases, 10th revision, ICD-10, F10.2).
2. Alcohol withdrawal state (ICD-10, F10.3).

Therapeutic intervention

Pharmacological treatment

The patient was initially treated with chlordiazepoxide 60 mg/day for alcohol withdrawal. Within 24 hours of administration of chlordiazepoxide, he developed multiple vesicles over hyperpigmented erythematous targetoid macules located over both upper limbs, anterior and posterior trunk, and back of neck (Figure 1). There was no history of any constitutional symptoms. There was no involvement of any of the mucosal surfaces. Relevant hematological and biochemical investigations, including blood counts, liver/renal functions, blood glucose, lipid/thyroid profiles were repeated, and the results were within normal boundaries.

Concomitant diagnosis

A dermatology evaluation was conducted, and the patient was diagnosed as a case of GBFDE, with chlordiazepoxide being the offending drug. As per ICD-11, the patient was diagnosed as "Other specified adverse cutaneous reactions to medication" (EH7Y). The Adverse Drug Reaction Probability Scale (ADR Probability Scale) score for chlordiazepoxide was 7 (probable Adverse Drug Reaction, ADR [9]).

Follow-up and outcomes

Chlordiazepoxide was discontinued immediately. The patient was prescribed oral prednisolone (50 mg/day) and topical clobetasol cream (0.05% weight/weight) for 7 days. His lesions resolved gradually over a period of one week, leaving behind dark grey hyperpigmented lesions. He was advised to avoid chlordiazepoxide lifelong. His withdrawal was managed with oral diazepam, with no recurrence of dermatological symptoms. Subsequently, the patient was treated for ADS with psychosocial interventions and naltrexone (50 mg/day), without any ADRs.

Prognosis

The patient demonstrated a favorable prognosis. Following the discontinuation of chlordiazepoxide and initiation of oral prednisolone and topical clobetasol, the skin lesions resolved completely within one week, leaving behind residual hyperpigmentation. No recurrence of GBFDE was observed during subsequent treatment, and the patient successfully completed his treatment for ADS. The patient was reviewed on a monthly basis in an outpatient setting for ADS, and he was noted to have remained abstinent over the next three months.

Timeline

The patient timeline is presented in Table 1.

DISCUSSION

Case report summary

This case report describes a 40-year-old male with a history of ADS, admitted for alcohol withdrawal management, who developed GBFDE following chlordiazepoxide administration. The patient initially developed transient vesicles on hyperpigmented erythematous targetoid macules, which resolved within one day of discontinuing chlordiazepoxide, leaving behind hyperpigmented lesions. The diagnosis was based on clinical criteria and confirmed with ADR Probability Scale score of 7, indicating a probable ADR. The patient was treated successfully with oral prednisolone and topical clobetasol, resulting in complete resolution of the lesions within a week.

Case report discussion

FDE is a delayed type IV hypersensitivity reaction, which occurs secondary to exposure to a causative agent. GBFDE is a rare and severe variant of FDE associated with blisters/erosions involving at least 10% of the BSA [10]. FDE has been linked to various medications, including anti-infective drugs such as β-lactam antibiotics, tinidazole, and acyclovir; analgesics like paracetamol, mefenamic acid, and metamizole sodium; non-steroidal anti-inflammatory drugs; anti-epileptic medications such as carbamazepine; psychoactive substances like barbiturates and codeine; and other agents such as allopurinol, contrast media, omeprazole, and loratadine [3]. Benzodiazepines such as chlordiazepoxide, lorazepam, and lormetazepam have also been implicated in the emergence of FDE, although rarely [11, 12]. Specifically, chlordiazepoxide triggers a variety of adverse cutaneous reactions, including urticaria, FDE, morbilliform erythema, systemic lupus erythematosus, drug-induced photosensitivity, purpura, and Stevens–Johnson syndrome [13, 14]. Blair in a case report in 1974 described a 48-year-old female on chlordiazepoxide (40 mg/day) who developed an erythematous maculopapular

Table 1. Patient chronology of disease development, key events and prognosis

Date	Key events	Condition
08 July 2024	Index patient voluntarily admitted in psychiatry ward to quit alcohol.	Patient diagnosed as a case of ADS and alcohol withdrawal state. Chlordiazepoxide 60 mg/day initiated.
09 July 2024	Developed multiple vesicles over erythematous hyperpigmented targetoid macules located over both upper limbs, anterior and posterior trunk, and back of neck.	Diagnosed as a case of GBFDE, with chlordiazepoxide being the offered drug. Chlordiazepoxide stopped immediately.
16 July 2024	—	Lesions resolved gradually over a period of one week, leaving behind dark grey huperpigmented lesions.
July–September 2024	—	For ADS treated with psychosocial interventions and naltrexone (50 mg/day). A monthly review was conducted in an outpatient setting, and it was noted that the patient maintained abstinence from alcohol for the following 3 months.

Note: ADS — Alcohol dependence syndrome; GBFDE — generalized bullous fixed drug eruption.

patch, 2.5 cm in diameter on the left side of her neck [15]. Chlordiazepoxide was discontinued, and she was treated with topical steroids and oral antihistamines, which led to a consequent improvement in the lesion. Upon reinstating chlordiazepoxide, the lesion returned to its erythematous and indurated state. The lesion again improved upon discontinuation of chlordiazepoxide. The author has, however, described the lesion as FDE rather than assigning the diagnosis of GBFDE [15].

Clinically, determining the culprit drug in the cases of FDE, especially those on polypharmacy, requires an oral provocation test, which involves administrating the putative offending drug, starting with a dose lower than the usual. However, the same procedure can trigger GBFDE and, hence, is contraindicated in patients who have had generalized forms of FDE [16]. A positive patch test over the previously affected area is a relatively safe course of action [16]. In the index case, the ADR Probability Scale score for chlordiazepoxide was 7 (probable ADR) [9]. The score was, however, spuriously low, as re-administration of the putatively offending drug is contraindicated in patients with GBFDE [16, 17]. Secondly, owing to the high mortality that accompanies the adverse reaction [4], chlordiazepoxide had to be abruptly stopped and any variation in the ADR (based upon an increased/decreased dose of the drug) could not be observed. Re-administration of the putative offending drug in ADRs with high mortality rates also comes with ethical considerations [16, 17].

GBFDE is a clinical diagnosis and generally does not require any biopsy [18]. A differential of Stevens-Johnson syndrome/toxic epidermal necrolysis was considered. The points in favor of GBFDE included rapid onset of symptoms (within 24 hours), presence of well-demarcated, marked hyperpigmented patches with adjacent skin being normal, characteristic absence of constitutional symptoms, and no mucosal involvement. However, some points against the diagnosis included no prior history of chlordiazepoxide use and no previous history of such reactions [17, 19].

In light of the rarity of GBFDE caused by chlordiazepoxide, the absence of prior reports, and the general predominance of antibiotics and non-steroidal anti-inflammatory drugs as causative agents, it is imperative to consider the possible mechanisms underlying this adverse reaction. One plausible explanation could be that chlordiazepoxide acts as a hapten, forming a complex with proteins in the skin, which subsequently triggers a delayed type IV hypersensitivity reaction. Another possibility is the role of genetic predisposition, which may make certain individuals more susceptible to benzodiazepine-induced immune-mediated reactions. Further research, including pharmacogenomic studies, is warranted to elucidate the mechanisms under chlordiazepoxide-induced GBFDE and to identify patients at higher risk of such ADRs.

The mainstay in the treatment of FDE/GBFDE is identifying and discontinuing the offending drug; in the majority of cases, no further treatment is needed [2]. Topical and oral corticosteroids (like prednisolone), and cyclosporine, have also been tried with success [2]. There is a lack of clinical trials evaluating the effectiveness of supportive care alone compared to treatments such as oral or topical steroids and cyclosporine in the treatment of GBFDE. It remains unclear whether these therapies accelerate symptom resolution or reduce mortality rates in comparison to a simple discontinuation of the causative drug [2].

Strengths and limitations

This case report has several strengths. It documents a rare case of ADR — GBFDE — caused by chlordiazepoxide, a widely used benzodiazepine. The report highlights the importance of early identification, prompt drug discontinuation, and effective management in achieving a favorable outcome. Additionally, it provides valuable insights into the potential cutaneous adverse effects of benzodiazepines, expanding the scope of clinical awareness.

However, there are limitations to this report. First, the transient nature of the vesicles meant they had resolved before photographic documentation could be obtained, reducing the illustrative value of the case. While the absence of bullae in the provided images could raise diagnostic questions, the overall clinical presentation, the response to the discontinuation of the drug, and the characteristic pattern of residual hyperpigmentation confirm the diagnosis. Second, the inability to perform a drug re-challenge due to ethical concerns limits a definitive confirmation of chlordiazepoxide as the causative agent. Lastly, the absence of histopathological examination/immunological studies of the lesions further constrains the case's scientific depth.

Despite these limitations, this case adds to the existing body of knowledge by reporting a novel association and underscores the need for vigilance when prescribing chlordiazepoxide.

CONCLUSION

This case report highlights the possibility of chlordiazepoxide as a rare, but potential, trigger of GBFDE. To the best of our knowledge, no prior reports have mentioned the same. We also recommend that clinicians maintain a high degree of clinical alertness when treating patients with chlordiazepoxide for developing GBFDE, owing to its rarity and potentially lethal outcome. This is even more the case in those patients who are being administered comparatively high doses of chlordiazepoxide (such as patients in alcohol withdrawal state). We also recommend the use of oral prednisolone and topical clobetasol in managing cases of chlordiazepoxide-induced GBFDE.

Informed consent: Informed consent was provided by the patient on 30 Jul 2024, prior to publishing this article. The participation of the patient was voluntary, and every step has been taken to maintain the patient's confidentiality and anonymity.

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