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Case Report

A RARE ADVERSE EFFECT OF CLOBAZAM INDUCED RASH IN A CHILD WITH FIRES (FEBRILE INFECTION WITH REFRACTORY EPILEPSY SYNDROME)

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ABSTRACT

Clobazam, an aromatic antiepileptic drugs and its active metabolite desmethylclobazam, has high affinity and agonistic activity on gamma-aminobutyric acid receptors resulting in suppression of abnormal and excessive activity of neurons. The reported incidence of maculopapular rash with Clobazam is <1%. A 13-year-old male with a diagnosis of febrile infection-related epilepsy syndrome developed a generalized erythematous maculopapular rash the next day following the introduction of Clobazam. Following this event, Clobazam was stopped and reintroduced after 17 days. However, the rash did not appear after its reintroduction. It was observed that the patient was on Fluconazole when the rash appeared. Fluconazole being a strong CYP2C19 inhibitor, results in an increased level of active metabolite, desmethylclobazam, which probably could have caused the rash. According to the World Health Organization, Uppsala Monitoring Centre Criteria, causality assessment was found to be probable. Adverse drug reaction was recorded and reported.

Keywords: Clobazam, Febrile infection-related epilepsy syndrome, Rash, Fluconazole.

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INTRODUCTION

Febrile infection-related epilepsy syndrome (FIRES) is a sudden-onset chronic epilepsy syndrome. The seizures and irreversible neurological damage develop between 24 h and 2 weeks after an acute febrile infection like an upper respiratory illness [1].

It progresses to a continuous state of status epilepticus which is resistant to conventional treatment; called refractory seizures or refractory epilepsy. The outcome is generally very poor and the children who survive can suffer neurological impairment and significant cognitive delay [2].

There is currently no specific treatment therapy for FIRES and there has been varying and inconsistent success with traditional anticonvulsants, immunoglobulin, and steroids.

Clobazam was introduced by the Food and Drug Administration as an add-on treatment for seizures associated with Lennox-Gastaut Syndrome in adults and children 2 years or older. It is a benzodiazepine. It works by increasing the action of gamma-aminobutyric acid which suppresses the abnormal and excessive activity of the nerve cells in the brain. The incidence of maculopapular rash with Clobazam is around 1%. It can cause rare but serious skin reactions called Stevens-Johnson Syndrome and toxic epidermal necrolysis [3,4].

Fluconazole is an antifungal drug that has been noted to inhibit CYP3A4 and CYP2C9 isoenzymes [5,6]. However, clinically significant drug interactions may occur only in certain patients, depending on several individual characteristics, such as genetics, health, nutrition, age, and concomitant drug administration.

Some studies have shown that the potential for drug-drug interaction increases as the number of prescribed drugs increases [7].

CASE REPORT

A 13-year-old boy diagnosed with FIRES with sepsis presented in the Neurology Department. He developed an Erythematous blanching maculopapular Rash over his trunk, face, and upper and lower limbs on the 5th day of admission which was suspected to be drug-induced (Fig. 1).

After a detailed drug history review, Clobazam was implicated for the rash because of temporal association (Clobazam started 2 days before the onset of the rash).

Clobazam was stopped and the rash subsided within a few days. Reintroduction of Tablet Clobazam 5 mg BD after 17 days did not result in any rash.

DISCUSSION

It was observed that the patient was also on Fluconazole for some fungal infection during that period when Clobazam was started for the 1st time following his admission. It was further observed that a drug interaction exists between fluconazole and clobazam. Fluconazole is a strong CYP2C19 inhibitor that can result in the increased level of the active metabolite, desmethylclobazam (Fig. 2).

The half-life of N-desmethylclobazam is 50 h whereas half-life of clobazam is only 18 h. This probably could have caused the rash.

After a detailed drug history review, clobazam was implicated for the rash because of temporal association.

According to the World Health Organization and Uppsala Monitoring Centre Criteria, causality assessment was found to be probable.

Our findings are also consistent with several other articles published [8,9]. A case of potential drug interaction between Clobazam and etravirine based antiretroviral therapy was also observed [10].

Fluconazole also has been reported to have drug-drug interactions with other different antiepileptic drugs. Fluconazole-induced symptomatic phenytoin toxicity was observed in patients receiving high doses of the drug in a study [11].

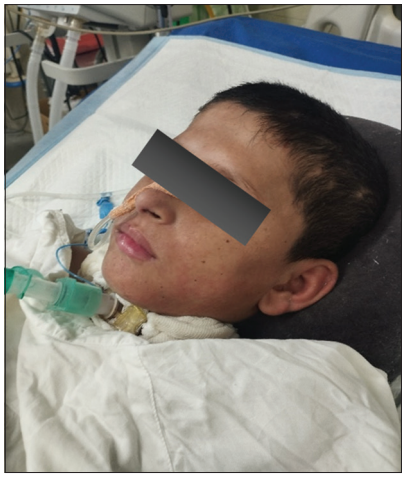

Fig. 1: Erythematous rash over the face

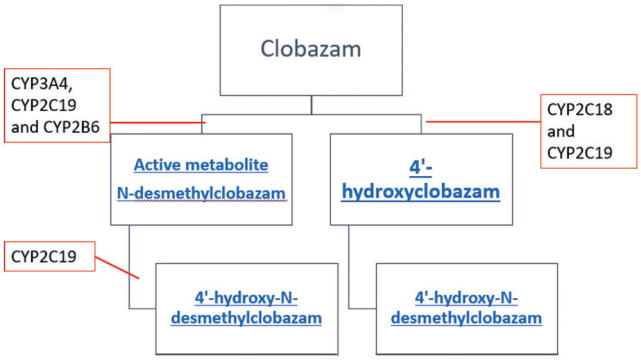

Fig. 2: Fluconazole effect on PK of Clobazam

In another study, a nearly twofold increase in plasma Carbamazepine levels was noted when administered with fluconazole. Following the withdrawal of fluconazole, the patient reported that all her symptoms disappeared and Carbamazepine plasma levels returned to normal limits [12].

CONCLUSION

Caution needs to be maintained while starting fluconazole with Clobazam in critically ill patients as it has the potential to cause drug interactions because of the inhibition of cytochrome enzymes CYP3A4, CYP2C9, and CYP2C19. It is recommended to do therapeutic drug monitoring to properly do dosage adjustments and thereby avoid any untoward side effects.

CONFLICTS OF INTEREST

There were no conflicts of interest among the authors.

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The authors did not receive any funding for the study.

INFORMED CONSENT

Written informed consent was obtained from the patient's guardian

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