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CASE REPORT

An Interesting Case of Carbamazepine-Induced Stevens–Johnson Syndrome

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Abstract

A 29-year-old Black female patient was admitted to a psychiatric ward with symptoms of major depressive disorder with psychosis. The patient was started on amitriptyline 50 mg/day and haloperidol 10 mg/day. On day 4 post-admission, the preferred first-line antidepressant, fluoxetine, became available and the patient was switched from amitriptyline to fluoxetine 20 mg/day. On the same day, the dose of haloperidol was reduced to 5 mg/day. Thirteen days post-initiation of these medications the patient became talkative, associated with emotional lability, an expansive mood, irritability and restlessness. The working diagnosis was changed to bipolar affective disorder in the manic phase. Fluoxetine was discontinued and carbamazepine 600 mg/day was added to the patient's treatment regimen. Her manic symptoms started to resolve; however, 14 days post-initiation of carbamazepine, the patient had a fever; itchy, discharging eyes; respiratory distress; generalised symmetrical erythematosus rash; buccal ulceration; and conjunctival injection with difficulty opening her eyes. Carbamazepine was immediately discontinued and the patient received intravenous fluid resuscitation. The patient recovered considerably after 12 days of symptomatic and supportive management, and was transferred back to the psychiatric ward for the continuation of bipolar disorder management. Lithium therapy was instituted and the patient was subsequently discharged. Using the Algorithm of Drug causality for Epidermal Necrolysis (ALDEN) Stevens–Johnson Syndrome/toxic epidermal necrolysis (SJS/TEN) drug causality scoring system, carbamazepine and fluoxetine were evaluated as 'very probable' and 'possible' causes of SJS, respectively, in this patient. Fluoxetine-induced SJS was considered on account of previous case reports, however no evidence of causality was found in this patient. Consecutive administration with a potential increase in carbamazepine due to inhibition of cytochrome P450 (CYP) 3A4 metabolism by fluoxetine was also not ruled out. A diagnosis of carbamazepine-induced SJS was made and was considered an idiosyncratic adverse drug reaction.

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Key Points

Stevens–Johnson syndrome (SJS) is one of the most severe types of cutaneous adverse reactions to drugs, with high morbidity and mortality rates.

Prompt recognition and adequate symptomatic and supportive management of SJS is necessary when prescribing known SJS-inducing medications such as carbamazepine.

Careful consideration is needed when prescribing multiple psychotropic drugs with a known risk for causing SJS.

Introduction

Severe cutaneous adverse drug reactions include a serum sickness-like reaction, acute generalised exanthematous pustulosis (AGEP), drug reaction with eosinophilia and

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systemic symptoms (DRESS) and epidermal necrolysis [1]. Epidermal necrolysis spectrum eruptions such as Stevens–Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN) are considered a continuum and share the same pathogenesis. They are only differentiated on the body surface area by epidermal detachment [2]. Epidermal detachment of < 10%, 10–30% and > 30% are designated as SJS, SJS/TEN and TEN, respectively [2, 3]. The mortality rate ranges from 1 to 5% for SJS, and 25 to 35% for TEN [2].

SJS and TEN are rare severe cutaneous reactions with annual incidences of 1.2–6 and 0.4–1.2 per million people, respectively [4, 5]. The common cause of SJS/TEN is drug exposure, while infections, contrast media, and vaccinations are mainly linked to SJS. Drugs commonly associated with the development of SJS/TEN include cotrimoxazole, nevirapine, allopurinol, sulfasalazine, phenytoin, phenobarbital, lamotrigine, and carbamazepine [1]. The estimated incidence of cutaneous adverse drug reactions (CADRs) to psychotropic medications among psychiatric inpatients is 2–5% [6]. Lange-Asschenfeldt et al. observed that antiepileptic drug (AED) mood stabilizers accounted for the highest CADR rate as a drug group, followed by antidepressants, while antipsychotics were the least commonly involved medications in CADRs [6]. Psychotropics with a high risk of epidermal necrolysis are carbamazepine, lamotrigine and phenobarbital [3]. Recent studies have also reported on selective serotonin reuptake inhibitor (SSRI)-induced epidermal necrolysis, and have implicated fluoxetine, paroxetine, fluvoxamine and mirtazapine [7–11]. There is no documentation of epidermal necrosis with concurrent administration of an SSRI and carbamazepine; therefore, we present a patient with bipolar affective disorder who developed SJS following consecutive administration of fluoxetine and carbamazepine.

Case Presentation

A 29-year-old Black female patient was admitted to the psychiatric unit with a 2-day history of disorganised behaviour, selective mutism, paranoid delusions, and auditory and visual hallucinations. The patient had been noted to be socially withdrawn with a depressive affect and had attempted suicide the day prior to her presentation to the psychiatric unit. This was her index psychiatric admission. The patient had no significant past medical history and no known drug allergies. An initial diagnosis of major depressive disorder with psychosis was made and the patient was started on amitriptyline 50 mg/day and haloperidol 10 mg/day. The patient was initially prescribed amitriptyline due to the unavailability of fluoxetine at the psychiatric unit at the time of admission. On day 4, the patient was switched from amitriptyline to fluoxetine 20 mg/day and the dose for haloperidol was reduced to 5 mg/day.

Thirteen days post-initiation of medications, the patient became talkative and had emotional lability and an expansive mood associated with irritability and restlessness. The working diagnosis was changed to bipolar affective disorder in the manic phase. Fluoxetine was discontinued and carbamazepine 600 mg/day was added to her treatment regimen. Her manic symptoms started to resolve; however, 14 days post-initiation of carbamazepine, the patient had a fever and itchy, discharging eyes. On examination she was in minimal respiratory distress, with a generalised symmetrical, erythematosus rash more marked on the face, upper limbs and chest. Her face was swollen, with bullae noted on her neck and chest. In addition, she had an associated buccal ulceration and conjunctival injection with difficulty opening her eyes. Her temperature was 38.2 °C, with SpO_2 of 97%, a blood pressure recording of 81/49 mmHg and a regular pulse of 108 beats/min. Vesiculobullous lesions were observed over the course of the admission, with sloughing of skin, especially on the chest and face around the lips.

Routine laboratory assessments showed normal blood counts without hypereosinophilia. Hepatic enzyme levels, renal function, and serum electrolyte levels were all within normal limits, and a serological test was negative for HIV. A diagnosis of SJS secondary to carbamazepine exposure was made. Evaluation of the SCORE of Toxic Epidermal Necrosis (SCORTEN) score on day 1 indicated a score of 0. No skin biopsy, blood or urine cultures were conducted.

Carbamazepine was immediately discontinued and the patient received intravenous fluid resuscitation. She was subsequently transferred to the medical ward where haloperidol 5 mg/day was maintained and supportive treatment was performed: the patient was kept warm, had careful protection of the eroded areas and non-intravenous hydration. Treatment for SJS included a hydrocortisone 100 mg stat dose, diazepam 10 mg twice daily, ceftriaxone, tetracycline eye ointment, and antiseptic mouth wash. The patient recovered completely after 12 days and was transferred back to the psychiatric ward, where lithium 500 mg/day was instituted. Eighteen days later, the patient was discharged on haloperidol 5 mg/day and lithium 500 mg/day; however, she was lost to follow-up and we cannot comment further on her clinical status.

Discussion

Carbamazepine is a well-known causative agent of drug-induced SJS among psychotropics [3]. Rare cases of SSRI-induced epidermal necrolysis, i.e. SJS and TEN, have been described in the literature [7–11]. To our knowledge, no cases of epidermal necrolysis have been described with coadministration of carbamazepine and an SSRI. In the case presented, the patient had been taking carbamazepine for

14 days after discontinuing fluoxetine. The temporal relationship between the development of SJS after the addition of carbamazepine suggests that carbamazepine was the causative agent. Although the median latency period (interquartile range) for the development of SJS with carbamazepine is 15 days (12–20) [12], latency periods of 4 weeks have also been reported [13]. The latency period for SSRI-induced SJS is 1–3 weeks. Using the Algorithm of Drug causality for Epidermal Necrolysis (ALDEN) scoring system for SJS/TEN, carbamazepine scored +6 and fluoxetine scored +2. Therefore, carbamazepine and fluoxetine were considered 'very probable' and 'possible' causes of SJS, respectively, in our patient [14].

Carbamazepine-induced SJS has long been thought of as an idiosyncratic, dose independent, unpredictable adverse event specific to an individual [15]; however, current evidence indicates that carbamazepine-induced SJS/TEN is a predictable, specific, delayed hypersensitivity immune reaction involving human leukocyte antigen (HLA) alleles specific for carbamazepine and other drugs in defined populations [16]. HLA-B*15:02 and HLA-B*31:01 have been associated with carbamazepine-induced SJS in Asian (Han Chinese, Thai, Indian and Malaysian) and Caucasian (and Japanese) populations, respectively [17–19]. Recent evidence suggests this possibility, as shown by the phenytoin and nevirapine-induced SJS/TEN associated with reduced drug clearance due to metaboliser enzyme polymorphisms [20, 21]. However, we were not able to genotype our patient for HLA alleles, therefore we cannot confirm the involvement of the phenotype-specific characteristics of the patient that might have contributed to the development of SJS. Although association with specific HLA genotypes may be necessary, it is not sufficient for the development of SJS/TEN [18]. Other factors such as the individual variation in drug metabolism or clearance, HIV-1 seropositivity, polypharmacy, and competitive drug inhibition may also play an important role in SJS/TEN development with carbamazepine [1, 18, 22, 23].

It has been postulated that no biologic effect is dose-independent [24] and that immune-mediated reactions only occur when a critical dose threshold has been reached [15, 25]. The maximum incidence for idiosyncratic reactions is often at a dose below the therapeutic range and remains constant within the therapeutic range [24]; however, this biologic dose-dependency principle (and possibly immune tolerance) is used successfully in desensitisation protocols for the safe introduction of medicines known to have idiosyncratic reactions [15, 24, 25]. Given the current understanding of idiosyncratic reactions, a potential increase in carbamazepine plasma concentration due to CYP3A4 inhibition by fluoxetine and norfluoxetine may have reached the threshold for the immune-mediated carbamazepine-induced SJS in our patient, leading to the observed adverse reaction [25, 26]. Increases in plasma carbamazepine or its metabolites increases the likelihood of adverse events, and possibly SJS, as occurs with phenytoin [27, 28]. It is possible that prior administration with fluoxetine may have increased the risk for SJS in our patient. The inhibitory capacity on CYP3A4 substrate clearance can persist up to 3 weeks post administration of fluoxetine due to the long half-life of norfluoxetine [29]. In our patient, carbamazepine was administered 14 days after fluoxetine was discontinued; however, we were unable to measure plasma concentrations of carbamazepine to confirm that competitive inhibition of metabolic enzymes by fluoxetine or norfluoxetine was involved in the development of SJS in our patient. Therefore, we cannot conclude that prior administration of fluoxetine may have increased the risk of carbamazepine-induced SJS.

Although epidermal necrolysis is rare with the use of SSRIs, several case reports have been documented for SJS or TEN with mirtazapine, fluoxetine, fluvoxamine and paroxetine [6–10]. Many of the reported cases have occurred in female patients who had received an SSRI for a duration ranging from 3 to 14 days. In our case, the patient had discontinued fluoxetine for 14 days when she developed SJS. However, fluoxetine and its major metabolite norfluoxetine have long elimination half-lives of 1–4 days and 7–15 days, respectively [30]. Although it is possible that fluoxetine or its metabolite norfluoxetine was involved in the development of SJS in our patient, it is more likely that the SJS was caused by carbamazepine and not by fluoxetine.

Conclusions

Carbamazepine-induced SJS is an idiosyncratic reaction; however, current evidence suggests that HLA genetic predisposition, drug structure, the patient's metabolic characteristics and T cell clonotypes need to be aligned for SJS to occur [18, 27]. More research is needed in African populations to delineate the pharmacogenomic risk alleles and to then provide relevant pre-prescription pharmacogenetic tests, as happens with people of Asian ancestry [19]. Clinicians should be aware of cutaneous adverse reactions due to psychotropic medications, particularly with AED mood stabilizers.

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Author Contributions JTM and GM collected the clinical information about the case. JTM drafted the manuscript, and SK and DC critically reviewed and revised the manuscript. All authors read and approved the final version submitted for publication.

Compliance with Ethical Standards

Conflict of Interest Josiah Tatenda Masuka, Garikai Muzopambwa, Star Khoza and Dixon Chibanda have no conflicts of interest that are directly relevant to the contents of this study.

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Ethical Approval This case report was approved by the Medical Research Council of Zimbabwe (Ref: MRCZ/E/193). All patient data were de-identified.

Consent to Participate Written informed consent was obtained from the patient for publication of this case report, a copy of which may be requested for review from the corresponding author.

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