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Successful use of carbamazepine in a patient with drug rash with eosinophilia and systemic symptoms

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Abstract

Drug rash with eosinophilia and systemic symptoms (DRESS) is a serious adverse drug reaction with a high mortality rate. Discontinuation of the causative agent is the primary treatment. History of DRESS may put patients at higher risk of future episodes; however, cross-reactivity between various medications is not well established. An 18-year-old African American male with a history of bipolar I disorder with psychotic features was admitted for mania on his home dose of divalproex. After 1 week, olanzapine was added for refractory symptoms, but due to elevated creatinine phosphokinase (CPK), it was subsequently discontinued, and he was started on lorazepam and lithium. One week later, the patient was transferred to the intensive care unit with elevated CPK, fever, thrombocytopenia, elevated serum creatinine, hypotension, diarrhea, mild rigidity, bilateral inducible ankle clonus, and a rash. All medications were discontinued except for lorazepam. The skin pathology report was consistent with a drug eruption, and he was started on prednisone. Given continued symptoms of mania, carbamazepine was initiated. After clinical and laboratory improvement, the patient was discharged on hospital day 59 with instructions to continue carbamazepine and lorazepam. A MEDLINE search revealed no published case reports of the successful use of carbamazepine in a patient with a history of DRESS. Information regarding cross-reactivity between medications is limited primarily to aromatic antiepileptics. In our case report, carbamazepine was successfully used in a patient with a recent episode of DRESS during olanzapine, lithium, and valproate use.

Keywords: DRESS, carbamazepine, olanzapine, lithium, valproate

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Background

Drug rash with eosinophilia and systemic symptoms (DRESS) is a rare but serious idiosyncratic drug reaction with an incidence of 0.1 to 1 per 1000 individuals taking high-risk medications and an associated mortality rate of 10% to 20%.[1,2] Medications most commonly implicated with DRESS include allopurinol (18%); sulfonamides (12%); antibiotics (11%); and aromatic antiepileptics (35%), such as carbamazepine (20%), phenytoin (7%), lamotrigine (7%), and phenobarbital (1.7%).[1] The diagnosis of DRESS is difficult due to the overlapping symptoms between DRESS and other serious conditions, such as serotonin syndrome and neuroleptic malignant syndrome (NMS).[1,3,4] The clinical presentation of DRESS is characterized by fever, rash, lymphadenopathy, internal organ involvement

(eg, liver), and hematologic abnormalities (eg, eosinophilia).[1,2] A biopsy can help confirm the diagnosis; however, the histopathologic features of the rash often show variable inflammatory patterns.[5] Drug rash with eosinophilia and systemic symptoms typically occurs 2 to 8 weeks following initiation of the culprit medication.[1] The pathogenesis is not well understood but thought to be related to one of the following mechanisms: a delayed immunologic reaction, a transient state of immune suppression, and/ or reactivation of latent herpes virus infections. Discontinuation of the causative agent is the primary treatment.[2] Following an episode of DRESS, choosing alternative pharmacological therapies must be done cautiously as there are limited data available regarding cross-reactivity between various medications. In this case report, we discuss a patient who was initiated on carbamazepine after the development of DRESS following recent exposure to divalproex sodium, lithium, and olanzapine.

Case Report

Initial Presentation

An 18-year-old African American male with a history of bipolar I disorder with psychotic features was admitted to inpatient psychiatry for mania. Three days prior to presenting, he restarted divalproex sodium delayed release (1000 mg at bedtime). He presented disorganized, distractible, sexually preoccupied, and hyperverbal. Urine toxicology was negative.

Pertinent Past Medical/Psychiatric History

The patient had no known drug allergies. However, during a psychiatric admission 4 years prior, he experienced creatinine phosphatase kinase (CPK) elevations on risperidone (CPK up to 3674 IU/L). Following the discontinuation of risperidone, he was initiated on olanzapine and chlorpromazine, but this resulted in repeat CPK elevations leading to the discontinuation of all antipsychotics and requiring combination therapy with lithium, lorazepam, and divalproex. Again, CPK concentrations increased, and he developed a fever and tachycardia in the presence of a transient macular rash. All medications aside from lorazepam were stopped, and electroconvulsive therapy (ECT) was initiated. With continued ECT, taper of lorazepam, and reinitiation of divalproex, his disorganization, agitation, and psychotic features improved, and his labs normalized.

Hospital Course

On admission, the patient's home dose of divalproex was continued (Table 1). From hospital day (HD) 1 to HD 10, he received as needed oral doses of olanzapine every other day and received one dose of intramuscular olanzapine for acute agitation. On HD 10, olanzapine 5 mg oral daily was scheduled and increased to 10 mg by HD 12. On HD 15, CPK was elevated, and his olanzapine was decreased to 2.5 mg daily. Creatinine phosphatase kinase continued to rise (3642 IU/L on HD 22), and olanzapine was discontinued as a precaution based on history of possible NMS with antipsychotics despite absence of other symptoms of NMS. This elevation in CPK was attributed to an episode of agitation requiring physical restraints and a dose of intramuscular olanzapine. He continued to appear manic and was subsequently started on lithium and lorazepam. He remained clinically stable, and his CPK down-trended to 718 IU/L. On HD 28, he developed a fever, lymphadenopathy, diarrhea, diffuse abdominal pain, and an episode of dark emesis, and his CPK increased to 1435 IU/mL. Additionally, liver function enzymes, white blood count, and serum creatinine were significantly elevated from baseline. He became increasingly tired and confused, and all psychotropic medications aside from lorazepam were discontinued due to concern for NMS. He was transferred to general medicine where he developed a morbilliform rash on his chest, trunk, arms, and legs. Because serotonin syndrome was not able to be ruled out, he was started on cyproheptadine and continued until the punch biopsy results returned consistent with drug eruption (perivascular lymphocytic inflammation with mild dermal hemorrhage). Dermatology, psychiatry, and hematology consult services agreed on a suspected diagnosis of DRESS, and he was initiated on a prednisone taper. Given the anticipated prolonged corticosteroid taper, sulfamethoxazole-trimethoprim was added for prophylaxis against *Pneumocystis* pneumonia based on a statement by the American Thoracic Society.[6] His workup was negative for infection, hepatitis virus, and antinuclear antibody. As he improved medically, he began to exhibit grandiosity and mood lability concerning for reemergence of manic symptoms. Following initiation of carbamazepine on HD 34, the medication was slowly titrated, and his mood returned to baseline by discharge on HD 59. He was briefly rehospitalized 2 days after discharge due to residual symptoms in the context of psychosocial stressors, but no medication changes were made. During an outpatient follow-up, he continued to appear euthymic and all DRESS-related symptoms were resolved.

Discussion

The differential diagnosis in this case included DRESS, serotonin syndrome, sepsis, and NMS. Based on the punch biopsy results, eosinophilia, and improvement following corticosteroid administration, it was determined that DRESS was the most definitive explanation for this presentation. Additionally, he scored a 6 of 9 on the

TABLE 1: Patient summary

Day	Event
0	Continued home dose of divalproex sodium delayed release 1000 mg at bedtime
	Weight: 72 kg
	SCr: 0.9 mg/dL
	AST: 28 IU/L
	WBC: 12 000/μL
	Platelets: 186 000/μL
10	Olanzapine 5 mg intramuscular given for acute agitation
	Olanzapine 5 mg orally once daily scheduled
	CPK: 844 IU/L
12	Olanzapine oral increased to 10 mg daily
	CPK: 740 IU/L
	Valproic acid: 74.6 μg/mL
15	Olanzapine oral reduced to 2.5 mg daily
	CPK: 1374 IU/L
17	Haloperidol 5 mg intramuscular given once for agitation
	CPK: 631 IU/L
20	Valproic acid: 106.7 μg/mL
	CPK: 1319 IU/L
21	Olanzapine 5 mg intramuscular given for acute agitation
	Lorazepam 1 mg oral twice daily and lithium 300 mg oral twice daily initiated
	CPK: 1415 IU/L
22	Olanzapine discontinued
	CPK: 3642 IU/L
	Tmax: 36.7°C
26	CPK: 718 IU/L
	Valproic acid: 88 μg/mL
27	Tmax: 39.5°C
	BP: 89/51 mmHg
	Pulse: 125 BPM
	SCr: 1.3 mg/dL
	Platelets: 80 000/μL
	CPK: 1435 IU/L
	Valproic acid: 32.8 μg/mL
	Lithium: 0.38 mmol/L
	Diarrhea, abdominal pain, mild rigidity, bilateral inducible ankle clonus
	Morbiliform rash on trunk and legs
	Divalproex sodium and lithium were discontinued
29	Punch biopsy obtained
	CPK: 4618 IU/L
	Absolute lymphocyte count: 600/μL
	Cyproheptadine 12 mg once, followed by 6 mg every 6 h started
31	Punch biopsy results consistent with drug eruption/ reactive erythema
	Cyprohepatadine stopped
	Prednisone 1 mg/kg/d oral and SMX/TMP 800-160 mg 3 times weekly initiated
	AST: 525 IU/L
33	WBC: 33 200/μL (peak)
	Absolute eosinophils: 2700/μL (peak)
34	Carbamazepine 200 mg twice daily initiated
	Absolute lymphocyte count: 8000/μL (peak)
	Rash documented to be resolving
	CPK: 1499 IU/L
59	Discharged on carbamazepine 800 mg twice daily
	CPK: 161 IU/L
61-68	Readmitted to inpatient psychiatry
	WBC: 10 900/μL
	Absolute lymphocyte count: 3300/μL
	Absolute eosinophils: 0/μL
	Platelets: 187 000/μL
	SCr: 0.83 mg/dL
	AST: 27 IU/L
	CPK: 386 IU/L
	Carbamazepine concentration: 9.0 mg/L
84	Outpatient follow-up visit
	Mood appeared euthymic
	All DRESS-related symptoms resolved
	No labs obtained

AST = aspartate aminotransferase; BP = blood pressure; CPK = creatinine phosphokinase; DRESS = drug rash with eosinophilia and systemic symptoms; SCr = serum creatinine; SMX/TMP = sulfamethoxazole-trimethoprim; Tmax = maximum temperature; WBC = white blood count.

DRESS scoring system developed by Karduan et al,[1] which indicates a definite case of DRESS. However, the patient also met the diagnostic criteria for serotonin syndrome and NMS (Table 2). Divalproex, lithium, and olanzapine were subsequently discontinued. The patient was treated with corticosteroids based on treatment success in prior reports.[1,2]

Determining the causative agent was challenging as all 3 medications have been associated with DRESS. Divalproex has been implicated as a cause of DRESS and has the most published reports of DRESS among the medications that the patient was taking.[2] However, he previously tolerated divalproex monotherapy and historically only had adverse reactions when it was combined with antipsychotics or lithium. Lithium has been associated with DRESS in a limited number of case reports.[7,8] However, the patient was only taking lithium for 6 days prior to the onset of DRESS, making it an unlikely culprit.

TABLE 2: Differential diagnosis[a]

Category	DRESS[1]	Serotonin Syndrome[3]	Neuroleptic Malignant Syndrome[4]
Exposure	**Reaction suspected to be drug-related**	**Recent exposure to a serotonergic agent** No recent addition of a neuroleptic agent	**Recent exposure to dopamine antagonist**
Hematologic	**Hypereosinophilia** **Blood count abnormalities** **Lymphocytosis**	. . .	**Leukocytosis**
Organ involvement	**Involvement of at least one internal organ**	. . .	. . .
Neurologic function	. . .	**Altered mental status** **Agitation**	**Altered mental status**
Musculoskeletal	. . .	**Myoclonus** Hyperreflexia Tremor	**Elevated CPK** Severe muscle rigidity Tremor
Dermatologic	**Acute rash**	. . .	. . .
Other	**Lymphadenopathy** **Fever (>38°C)**	**Diaphoresis** **Fever (>38°C)** **Diarrhea** Shivering	**Fever (>38°C)** **Tachycardia** **Diaphoresis** **Elevated or labile blood pressure** Mutism

CPK = creatinine phosphokinase; DRESS = drug rash with eosinophilia and systemic symptoms.

[a]Bold indicates signs and symptoms the patient exhibited during hospital admission.

Symptoms began roughly 21 days after the first dose of olanzapine, which is consistent with the onset of DRESS reported in the literature.[1,2] Olanzapine is not an agent that has traditionally been associated with DRESS. However, in 2016, the US Food and Drug Administration[9] published a warning regarding the risk of DRESS associated with olanzapine following 23 cases of olanzapine-induced DRESS.

In addition to discontinuing the agent(s) that may have induced DRESS, it is recommended to avoid agents with similar structures because cross-reactivity between aromatic anticonvulsants may be as high as 80%.[2,10,11] Although less common, there are case reports of DRESS caused by nonaromatic psychotropic medications.[2] As valproate and lithium are not aromatic and structurally dissimilar to the aromatic anticonvulsant carbamazepine, cross-reactivity was unlikely.[12] There are some structural similarities between carbamazepine and olanzapine. In fact, 1 case report exists describing the cross-reactivity between these agents in a patient who developed DRESS.[13] Case reports[10,14-16] also describe secondary neosensitization to certain medications following DRESS induced by structurally different agents. Neosensitization is thought to be caused by a transient state of immunosuppression induced during the first episode of DRESS that may trigger a nonspecific immune system response leading to the inability to tolerate other drugs present at the time. In several reports of neosensitization, the agent that was related to the second hypersensitivity episode was initiated during the first episode of DRESS,[15,16] but this was not consistent in every case.[10,14,16] Although a positive history of DRESS is a major risk factor for future episodes, our patient was left with limited treatment options for his bipolar mania.[2]

The American Psychiatric Association (APA)[17] recommends lithium, valproate, or a second-generation antipsychotic as the first-line treatment of acute mania. Because the patient was receiving all of these medications prior to the development of DRESS and none could be excluded as the causative agent, it was difficult to determine the most appropriate agent for the treatment of his bipolar disorder. Alternative treatment options recommended by the American Psychiatric Association include carbamazepine and ECT. Based on the patient's preference, ECT was not considered at this time. A MEDLINE search revealed no published case reports of the successful use of carbamazepine in a patient with a history of DRESS from a nonaromatic medication. Although carbamazepine carries a relatively high risk of DRESS, it was determined to be the safest option. Additionally, sulfamethoxazole-trimethoprim (which has a relatively high rate of DRESS) was successfully used.

Conclusion

When patients have severe drug reactions, it is important to minimize risk of recurrence. Previous reports have demonstrated the cross-reactivity of certain psychotropic medications in causing DRESS. Ideally, alternative medications following an episode of DRESS should be structurally dissimilar and associated with a low risk of reaction. In this case, we were successfully able to use both carbamazepine and sulfamethoxazole-trimethoprim even though both have a relatively high rate of DRESS.

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