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Carbamazepine drug reaction involving high fevers during the COVID-19 era

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Abstract

Carbamazepine has demonstrated anticonvulsant properties and is used for a variety of indications in psychiatry and neurology. Total daily doses typically range from 200 to 1200 mg/d, generally divided into 2 doses. Carbamazepine has a broad side-effect profile but is not typically thought to produce high fevers in the absence of a hypersensitivity syndrome. This is a case of a probable adverse drug reaction to carbamazepine consisting of fever without severe major organ involvement. In this instance, a patient in a manic episode with psychotic features was briefly transferred to a COVID-19 unit to rule out coronavirus infection before the fever resolved.

Keywords: carbamazepine, adverse drug reaction, COVID-19, coronavirus, bipolar disorder, case report

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Background

Carbamazepine has demonstrated anticonvulsant properties; it blocks neuronal voltage-gated sodium channels and impacts GABA and glutamate release, though its precise mechanism of action remains unknown.[1] It is FDA approved[2] for the treatment of partial-complex seizures, generalized tonic-clonic seizures, mixed seizures, trigeminal neuralgia, and acute mania. Carbamazepine is typically prescribed at a dose of 200 to 1200 mg/d, given in 2 divided doses. Usual therapeutic plasma levels are between 4 and 12 µg/mL, although there is no clear relationship between plasma level and drug response.[3] Carbamazepine has a broad side effect profile including sedation, confusion, nausea, diarrhea, and benign leukopenia. In rare instances it can cause aplastic anemia, agranulocytosis, hepatotoxicity, Stevens-Johnson syndrome, and drug reaction with eosinophilia and systemic symptoms. However, it is not typically thought to cause fever in the absence of these more systemic hypersensitivity reactions.[4,5] Currently, because of the COVID-19 pandemic, fevers in hospitalized patients are typically treated as coronavirus infections until proven otherwise. This is a case of a hospitalized woman who developed a fever that reached 104.4°F. Because of her psychiatric symptoms, she initially refused a full workup and so was precautionarily transferred to a COVID-19 unit. Her fever developed 9 days after initiation of carbamazepine and completely resolved 3 days after discontinuation of the medication without any treatment other than acetaminophen.

TABLE: Temperature, oxygen saturation, and laboratory values recorded during hospitalization

Variable	Hospital Day								
Vital Signs and Biochemistry	16	17	18[a]	19	20	21	24[b]	35[b]	Reference
Max temp, F	100.2	102.0	104.4	102.4	100.3	100.3[c]	98.7	97.7	
Min O2 sat, %	95	96	91	90	R	R	96	99	
Covid PCR		Neg			Neg				
WBC, k/mL	...	4.1	3.9	...	3.3	...	3.1	5.1	3.5-10.5
Abs lymph, k/mL	...	1.0	0.9	...	0.8	...	1.6	1.3	1-4
CRP, mg/dL	...	1.4	2.0	...	3.4	...	0.7	<0.5	0-0.5
ESR, mm/hr	...	35	...	...	...	...	...	...	4-25
D-dimer, ng/mL	...	...	374	...	526	...	447	174	0-230
LDH, units/L	...	...	309	...	300	...	...	...	0-271
Procalcitonin, mg/mL	...	...	...	0.347	0.367	...	...	...	<0.065
Antinuclear antibody	...	...	...	...	Positive (1:1280)	...	...	...	Neg
SSA Ro antibody, units	...	...	...	>8.0	...	...	...	...	<0.9
SSB La antibody, units	...	...	...	>8.0	...	...	...	...	<0.9

Abs lymph = absolute lymphocyte count; CRP = c-reactive protein; ESR = erythrocyte sedimentation rate; LDH = lactate dehydrogenase; Min O2 sat = minimum oxygen saturation; R = refused; SSA = anti–Sjögren-syndrome type A; SSB = anti–Sjögren-syndrome type B.

[a]Last carbamazepine dose received in the morning.

[b]Several days omitted for brevity and clarity.

[c]Final recorded abnormal temperature during admission.

Case Report

A 52-year-old female with bipolar disorder and a past medical history of hypothyroidism was admitted to the psychiatric unit for the treatment of a manic episode. She had first been diagnosed with bipolar disorder in early adulthood and had taken lithium for most of the following 3 decades along with adjunctive mood stabilizers and antipsychotics. Prior to admission, she had been taking lithium carbonate CR 900 mg nightly, quetiapine 50 mg twice daily, and levothyroxine 125 mcg daily. She expressed deep ambivalence regarding psychiatric medications. While she initially agreed to increase quetiapine to target her worsening symptoms, on hospital day 4 she stopped taking the medication. On hospital day 8, she agreed to take carbamazepine—a medication which she had taken for several years previously. The medication was started at 200 mg twice daily and incrementally increased over 4 days to a dose of 400 mg twice daily starting on hospital day 12. During this period, she self-discontinued lithium, which left carbamazepine as her only scheduled psychotropic medication.

Over the hospitalization, the patient's mania worsened: she became more talkative, her affect became more irritable, and her thought process became characterized by a worsening flight of ideas. On hospital day 16, a carbamazepine trough level was ordered and accidentally drawn twice by the phlebotomist. It was measured as 11.5 μg/mL and 12.1 μg/mL. The patient had been taking carbamazepine 400 mg twice daily for 4 days, except for the evening dosage on hospital day 13 that she refused. Blood was drawn 10 hours after the last administration of the medication. That evening, she complained of a headache and was given acetaminophen. On hospital day 17, 9 days after initiation of carbamazepine, she developed a fever (see the Table and Figure for details) and the medical service was consulted for further evaluation. She complained of no other symptoms; a complete metabolic panel including liver function tests, complete blood count, urinalysis, and creatine kinase were all unremarkable, a COVID-19 PCR assay was negative, and c-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were mildly elevated. She refused carbamazepine that evening and overnight was given acetaminophen.

On hospital day 18, the patient took her scheduled morning carbamazepine and her fever increased to 104.4°F. She complained of headache and jaw pain, but her complaints were difficult to interpret given her increasing disorganization. She refused a repeat COVID-19 test, and the decision was made to transfer her to the medical floor. Inflammatory markers including d-dimer and lactate dehydrogenase were elevated as was a repeat CRP. A chest x-ray was notable for "minimal increase in the interstitial markings in both lungs and minimal linear atelectatic areas at the bases," according to the radiologist's report, but was otherwise unremarkable. A CT scan of the face, chest, and abdomen was ordered but

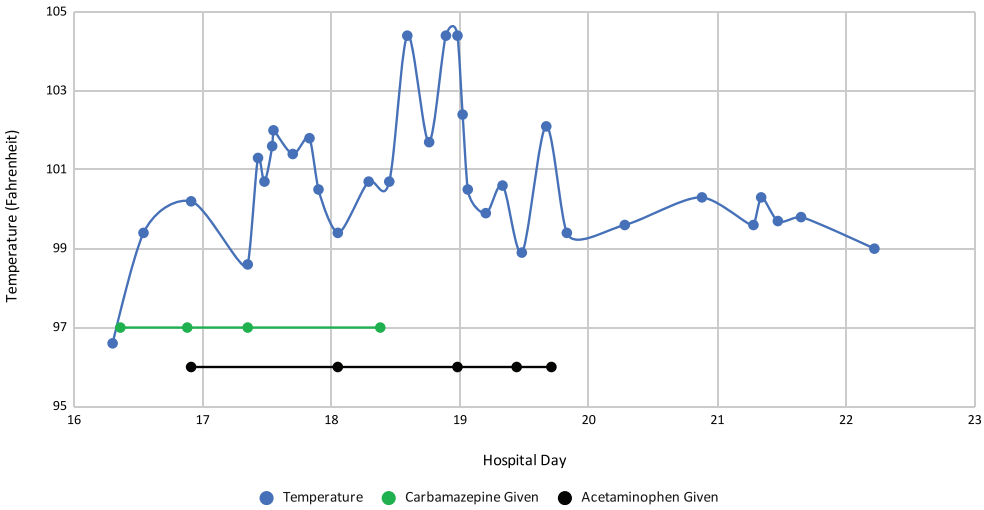

FIGURE: Progression of fever in relation to carbamazepine discontinuation

the patient refused. She also refused her evening dose of carbamazepine but accepted acetaminophen. That night, her measured oxygen saturation level decreased from 100% to 91% before returning to 94% over a 12-hour period.

On hospital day 19, the patient again refused her morning carbamazepine dose. Her measured oxygen saturation level normalized, but her fever continued, and she refused a repeat COVID-19 nasal swab, prompting the medical service to transfer her to a dedicated COVID-19 unit. Additional blood work was notable for an elevated procalcitonin level as well as an elevated antinuclear antibody with strongly positive anti–Sjögren-syndrome type A and B antibodies. She refused empiric antibiotic therapy. That evening, the on-call psychiatrist in consultation with the on-call pharmacist elected to hold carbamazepine to rule out medication side effect as the etiology of the fever. This decision left the day 18 morning dose of carbamazepine as the final dose administered to the patient. The patient accepted additional doses of acetaminophen.

On hospital day 20, she remained febrile and agreed to a repeat COVID-19 PCR swab, which was negative. On hospital day 21, her fever resolved, and on hospital day 22 she was transferred back to the psychiatric unit. The rheumatology service was consulted and noted that the patient had complained of dry mouth during their evaluation; they recommended she be reevaluated in 3 to 6 months for possible Sjögren syndrome once her mood stabilized given the presence of elevated anti-Sjögren-syndrome type A and B antibodies. However, they advised that this condition was unlikely to explain her fever. The allergy and immunology service was also consulted. They noted no evidence of rash on the patient's chest, back, abdomen, or extremities and advised that drug reaction was the most likely etiology.

The patient developed a mild lymphopenia which resolved within 2 weeks. She subsequently agreed to restart lithium and initiate olanzapine, and her psychiatric symptoms improved.

Discussion

During the COVID-19 pandemic, adverse medication reactions may be overlooked as a possible etiology of fever in hospitalized patients. In the current climate, all fevers are assumed to be due to COVID-19 until proven otherwise. On an inpatient psychiatric unit, possible COVID-19 infection is particularly concerning as those hospitalized are typically not isolated to their rooms and therefore the risk of an outbreak is far higher than on a general medical floor. In this case, the patient's laboratory work was notable for multiple abnormalities, including elevations in ESR, CRP, procalcitonin and d-dimer levels, all of which can be seen in individuals infected with COVID-19.[6] The patient's initial refusal to consent to a second COVID-19 PCR nasal swab further complicated the diagnostic picture and demonstrates the challenges of medically evaluating those suffering an acute exacerbation of severe mental illness. The patient ultimately did consent to a second PCR test, which was negative. Given that the patient tested negative for COVID-19 3 days apart using 2 different sample collections, it appears safe to conclude that these were indeed true negatives.

Anticonvulsant hypersensitivity syndrome secondary to carbamazepine has been previously described,[7] with symptoms typically including fever, rash, and internal organ involvement.[8,9] Of these symptoms, the individual described in this case report experienced only fever.

Additional forms of drug hypersensitivity were also considered: an IgE-mediated hypersensitivity reaction typically occurs within 2 hours of exposure to an offending agent and can manifest as rash, angioedema, bronchospasm, or hypotension. Immune complex deposition is typically characterized by the triad of fever, arthralgias, and rash. Cell-mediated hypersensitivity can present with mild cutaneous reactions, but it can also present as severe cutaneous adverse reactions such as Stevens-Johnson syndrome or toxic epidermal necrolysis. Internal organ involvement can also be seen including abnormal liver function and pulmonary manifestations.[10] While carbamazepine is associated with drug reaction with eosinophilia and systemic symptoms and pneumonitis,[11] the patient in this case did not develop eosinophilia, elevated liver enzymes, or respiratory symptoms. Her mild drop in oxygen saturation, which was noted only over the course of a single night, resolved spontaneously the following morning. It seems more likely that this transient recorded drop in oxygen saturation was due to poor monitor placement in an individual experiencing acute mania. She agreed to a skin examination the day after she returned to the psychiatric unit on hospital day 23, which was unremarkable. The lack of symptoms associated with the fever and the lack of cutaneous manifestations make allergic hypersensitivity unlikely, although prior studies have discussed that in 3% to 4% of patients, fever may be the lone manifestation of a hypersensitivity reaction.[12] A recent review[13] of drug fevers noted they typically occur 7 to 10 days after the initiation of the offending agent and can be associated with mild increases in ESR and lactate dehydrogenase, all of which were seen in this case. Elevated procalcitonin has also been reported in association with drug fevers,[14,15] as have elevations in CRP.[16]

Drug fever is a known entity that is characterized by the development of fever in association with the administration of a drug and disappearance upon the drug's discontinuation, typically without cutaneous manifestations. One study[16] examining all adverse drug reactions reported to the French National Pharmacovigilance Database from 1986-2007 found that only 0.05% of 323 340 cases could be classified as drug fevers. Of these drug fever cases, 3 were associated with carbamazepine administration. A letter[17] describing a single case of isolated carbamazepine-induced drug fever was also published in 1980.

The Naranjo algorithm[18] is a useful method to assess the likelihood of a causal relationship between an adverse event and a putative inciting agent. The algorithm includes 10 questions and is scored 0 to 13, allowing an adverse drug reaction to be classified as definite, probable, possible, or doubtful. A review of the clinical record indicates a Naranjo algorithm score of 6 in this case, indicating carbamazepine as the probable offending agent. The fever appeared after carbamazepine administration (+2), it improved after carbamazepine was discontinued (+1), there were no alternative causes that could have caused the event (+2), and the adverse event was confirmed by objective evidence including fever and laboratory abnormalities (+1). While the carbamazepine level was at the upper limit of normal (12.1 µg/mL), this level was measured only 4 days after a dose increase, 1 dose was missed during this period, and therefore the level did not represent a true steady state. It is possible that the patient's carbamazepine level was higher than the recorded level during the course of her fever. If the carbamazepine level was in the toxic range, the Naranjo algorithm score would increase from 6 to 7.

Conclusion

This case represents a probable carbamazepine-induced fever that was initially overlooked as medication-related on the inpatient psychiatric unit. During the current pandemic, when individuals suffering from severe mental illness develop coronavirus-like symptoms but refuse to participate in a full COVID-19 evaluation, it is important to consider medications as possible causative agents.

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