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Meloxicam-desmopressin drug-drug interaction producing hyponatremia

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ABSTRACT

Background: People with schizophrenia and medical comorbidities are often on multiple medications to manage their symptoms. Herein we present a case of drug-drug interaction (meloxicam and desmopressin), in a patient also on clozapine, that ultimately resulted in hyponatremia and seizure.
Methods: The patient provided consent to have his case published. We searched PubMed and after reviewing 321 articles, 11 were chosen for relevance.
Results: Meloxicam enhanced the adverse effect (hyponatremia) of desmopressin and was the likely culprit.
Conclusions: In a patient with higher ADH levels, as in our patient taking desmopressin, the addition of an NSAID could further increase water retention and worsen hyponatremia; indeed, meloxicam was the only new medication added to the patient's regimen, and a drug interaction calculator supports the desmopressin-meloxicam drug-drug interaction as the culprit. We urge clinicians to avoid the use of desmopressin in patients with schizophrenia as this can lead to water intoxication. As meloxicam may worsen desmopressin-induced hyponatremia and could result in seizure, one should avoid using NSAIDs in patients with schizophrenia whom are also prescribed vasopressin/desmopressin. Serum sodium levels should be closely monitored in patients with schizophrenia whose regimen includes desmopressin.

1. Introduction

Patients with schizophrenia and medical comorbidities are often on multiple medications to manage their symptoms. Herein we present a case of drug-drug interaction (meloxicam and desmopressin), in a patient also on clozapine, that ultimately resulted in hyponatremia and seizure. Patients with schizophrenia have a very high incidence of polydipsia which predisposes them to fluid overload, and many have some intellectual difficulties which may make them insensitive to the relatively subtle sensory signals that normally inhibit thirst in a hyponatremic individual. The addition of vasopressin to treat urinary incontinence, a common side effect of clozapine, even at small doses, can markedly reduce the kidney's ability to excrete a water load. Introduction of a non-steroidal anti-inflammatory drug (NSAID) to the regimen can remove the inhibitory effect of prostaglandins on antidiuretic hormone (ADH) activity and diminish free water excretion (Kim and Joo, 2007) even further, resulting in hyponatremia and seizure. In the literature, there is a dearth of information on polypharmacy induced hyponatremia, particularly in causing provoked seizures. This case contributes as a clinical aid for clinicians who find themselves in similar situations.

2. Methods

The patient provided consent to have his case published. We searched PubMed using the following key words and Boolean combinations as follows: 1) Clozapine and seizure; 2) (Clozapine and hyponatremia) AND (desmospressin OR lamotrigine OR meloxicam OR fluoxetine); 3) (Clozapine and seizure) AND (desmospressin OR lamotrigine OR meloxicam OR fluoxetine); 4) hyponatremia AND seizure AND meloxicam AND desmopressin. After reviewing 322 articles, 11 articles were chosen for relevance.

3. Results

3.1. Case

Mr. A is Caucasian gentleman in his 50's with chronic schizophrenia on clozapine and no history of seizure disorder. After admission to an inpatient psychiatric unit for suicidal ideation in the setting of acute on chronic bilateral knee pain, he developed his first lifetime seizure, with suspicion that it was due to hyponatremia as a medication side effect. Here we present his history, the diagnostic workup, and treatment considerations.

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Mr. A grew up in a home with 7 siblings and had special needs in school; he completed up to and inclusive of 12th grade. His father deceased in 2005. He resides in a community residential care home, and keeps in touch with family. A representative payee has helped him with his disability check since 1989. His cognitive and intellectual limitations have impacted his ability to learn. He smokes cigarettes 1 pack every other day, and denies any other substance use. He experienced multiple psychiatric hospitalizations leading to a diagnosis of schizophrenia, being treated in various state hospitals prior to transfer to the Department of Veterans Affairs (VA) system.

He has been on various medications, and has benefited from clozapine over the years, with improvement in aggression and psychotic symptoms. His clozapine dosage has been 225 mg by mouth every morning and 400 mg by mouth every bedtime for a decade. Fluoxetine 10 mg by mouth daily has been prescribed for mood symptoms. Regarding his third psychiatric medication, lamotrigine 100 mg by mouth twice daily, he has been told it was prescribed off-label for mood stabilization. He has Parkinson's disease with left upper extremity tremor. He has been treated for his hypertension, gastroesophageal reflux disease, asthma, and hyperlipidemia, and is on desmopressin 0.2 mg by mouth every bedtime for nightly urinary incontinence. Meloxicam was initiated for bilateral knee pain (Fig. 1) during his hospitalization and was the only new medication in his regimen, with his psychiatric medications being maintained at his home doses.

His medications were being administered at his community residential care home consistently. In late October, he started to experience acute on chronic bilateral knee pain and this worsened his mood symptoms, leading to inpatient psychiatric hospitalization for passive suicidal ideation. Upon consultation with his primary care physician, meloxicam 15 mg by mouth every day was initiated several days post admission for knee pain. He was also experiencing auditory and visual hallucinations of chronic nature since high school. He heard and saw a girl from his high school who would tell him he is "suicidal and retarded". She would disappear anywhere from minutes to hours on some

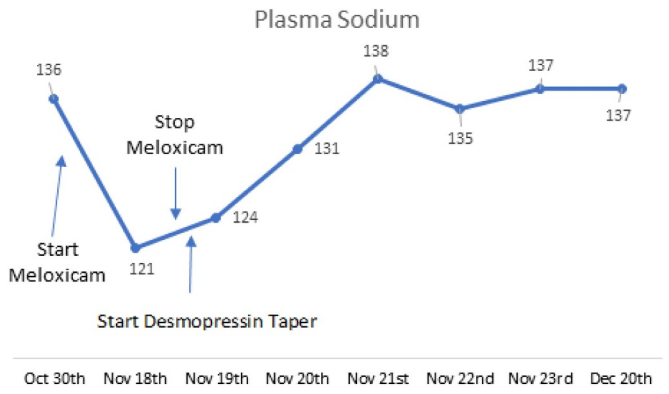

Fig. 1. Plasma sodium levels over time. Patient's sodium level prior to and inclusive of 10/31 (first data point, date of admission) were all within normal limits; first blue arrow from left indicates introduction of meloxicam 15 mg by mouth daily on 11/2 which was when patient was inpatient, for acute on chronic bilateral knee pain; there had been no other medication adjustments to his chronic psychiatric medications, which were continued*; 11/18 was the patient's first lifetime hyponatremia, which also occurred while inpatient; second blue arrow from left shows discontinuation of meloxicam; third blue arrow from left shows initiation of taper of desmopressin, leading to eventual normalization of sodium. Sodium normal reference range: 135–145 mmol/L. (*Desmopressin: unchanged dosage since 10/10/17 (0.2 mg by mouth every bedtime); lamotrigine: unchanged dosage since 9/12/17 (100 mg by mouth twice daily); Fluoxetine: unchanged dosage since 7/18/17 (10 mg by mouth daily); clozapine: unchanged dosage for a decade (400 mg by mouth every bedtime and 225 mg by mouth every morning)). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

days. While receiving inpatient care and continuing meloxicam, as per nursing, Mr. A experienced seizure activity described as full body involvement shaking, lasting approximately 20 s. He bit his tongue, but did not have signs of urinary or fecal incontinence. No head trauma or fall was reported. On workup the same day, his sodium was 121 mmol/L (normal range: 135–145). He was transferred to the medical intensive care unit (MICU), and neurology, psychiatry, and renal services were consulted. Given that he was hospitalized several weeks prior and had been in a controlled setting, substance intoxication and withdrawal were ruled out as potential causes of seizure. Meloxicam, as the new agent in his regimen, was deemed to be the culprit (Fig. 1).

During our interview, his mental status exam revealed a gentleman appearing older than his stated age, who was disheveled, mechanically stooped, and endorsed a slow shuffling gait when walking. He was dysarthric, with paucity of speech and poverty of thought. The thought content was suspected of having mild paranoia. His non-command auditory hallucinations persisted, however were not significantly bothering him today. His mood was "Eh…I'm okay; clozapine is working". His affect was congruent, blunted, with some irritability. He was at times able to engage in basic conversation, however had trouble following questions; he had poor insight and judgment, with limited impulse control, all of which appeared to be his baseline.

3.2. Case outcome

Mr. A experienced a witnessed general tonic-clonic (GTC) seizure and was found to be hyponatremic (121 mmol/L on admission). His computed tomography scan of the head was negative. He had a non-focal neurologic exam; magnetic resonance imaging was negative and findings on electroencephalogram showed no epileptiform activity as part of first time seizure workup. He had been on desmopressin as an outpatient for nightly urinary incontinence and was also taking his newly introduced meloxicam for knee pain. Meloxicam enhanced the adverse effect (hyponatremia) of desmopressin and was the likely culprit. Renal was consulted and provided guidance on management of the hyponatremia. It recommended gradual reduction of the desmopressin dose and withdrawal of this drug over 3–4 days; meloxicam was stopped. His free water intake was adjusted to allow the sodium to rise by 6–8 mM per day. In the medium term he was fluid restricted after 5 pm. Lamotrigine was continued for mood and seizure prophylaxis. Fluoxetine was stopped as no significant benefit for mood was reported from the patient. While clozapine seizure risk is positively correlated with dosage, Mr. A's clozapine regimen was stable for decades and not the culprit (Williams and Park, 2014; Foster and Olajide, 2005; Pisani et al., 2002; Mukku, S.S.R., et al., 2018; Muzyk et al., 2010). Literature suggests that having a seizure associated with concomitant clozapine use is not a contraindication for future use, and our patient was resumed on clozapine at his home dose (Williams and Park, 2014; Kikuchi et al., 201; Varma et al., 2011). He was continued on home acetaminophen and was advised to avoid meloxicam. He did not have any seizure activity while in the MICU or at discharge.

4. Discussion

Hyponatremia (serum sodium concentration <135 mmol/L) is a potentially serious electrolyte disorder, and certain drugs (e.g., thiazide diuretics, antidepressants, clofibrate, antiepileptics) have been implicated as a common cause of hyponatremia in non-hospitalized individuals (Demir et al., 2012). The sodium level of 121 mmol/L was likely due to contribution from the 200mcg standing nightly desmopressin dose, as desmopressin dosages as small as 10 mcg can increase the risk of hyponatremia; the absolute increased risk of hyponatremia with desmopressin use of greater than 10 mcg is 5.1% (Ebell et al., 2014). The nature of hyponatremia secondary to desmopressin is dilutional and is exacerbated when there are concomitant illnesses exacerbating fluid equilibrium. Symptomatic hyponatremia in these

situations is sometimes observed with prodromal symptoms such as headache, nausea, and vomiting (Lucchini et al., 2013).

NSAIDs diminish the normal inhibitory effect of prostaglandins on the activity of antidiuretic hormone and can therefore reduce free water excretion, leading to water retention and induction or exacerbation of hyponatremia (Demir et al., 2012). NSAIDs may cause severe or mild hyponatremia presumably in relation to the duration of drug use in people who have risk factors (advanced age, heart failure, use of diuretics, and hypovolemia) (Demir et al., 2012). In a patient with higher antidiuretic hormone (ADH) levels, as in our patient taking desmopressin, the addition of an NSAID could further increase water retention and worsen hyponatremia (Demir et al., 2012); indeed, meloxicam was the only new medication added to the patient's regimen, and a drug interaction calculator supports the desmopressin-meloxicam drug-drug interaction as the culprit. NSAIDs are widely prescribed medications used to manage everyday aches and pains and are also available over the counter. Hence, there have likely been similar cases of water intoxication in this setting that were likely missed, and their seizures were probably mistakenly attributed to clozapine. This could well have occurred in this case if the patient's NSAID had not been started while he was hospitalized.

We urge clinicians to avoid the use of desmopressin in patients with schizophrenia as this can lead to water intoxication. As meloxicam may worsen desmopressin-induced hyponatremia and could result in seizure, one should avoid using NSAIDs in patients with schizophrenia whom are also prescribed vasopressin/desmopressin. Serum sodium levels should be closely monitored in patients with schizophrenia whose regimen includes desmopressin.

Disclosure

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