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Case Report

SIADH and mixed delirium following the abrupt cessation of long-acting benzodiazepines: a case report

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Abstract

Benzodiazepines (BZDs) are among the most commonly used medications due to their efficacy and rapid onset of action. Although they offer significant therapeutic benefits in treating various psychiatric and neurological conditions, their clinical utility is limited by substantial risks, including dependency and withdrawal symptoms. The syndrome of inappropriate antidiuretic hormone secretion (SIADH) has been linked to BZD withdrawal. In this case report, we examine the case of an elderly female presented with a mixed delirium and SIADH following the abrupt cessation of long-term clonazepam therapy. To our knowledge, this is the second case that documents a link between SIADH and BZD withdrawal.

Keywords: SIADH; mixed delirium; benzodiazepines; withdrawal

Introduction

Benzodiazepines (BZDs) are psychoactive drugs that have a calming effect on the central nervous system [1]. They are widely used for their sedative, hypnotic, anxiolytic, and anticonvulsant propertie, however, their clinical use is limited by risks, including dependency and withdrawal symptoms [1]. The mechanism of BZDs action depends on enhancing the effect of the neurotransmitter gamma-aminobutyric acid (GABA), in particular GABA-A receptors. The $\alpha 1$ subunit is primarily associated with sedative and hypnotic effects while $\alpha 2$ and $\alpha 3$ are linked to anxiolytic and muscle relaxant effects. The therapeutic and side effects of benzodiazepines are mainly mediated through their action on GABA-A receptors [2].

As for BZD withdrawal symptoms, they can include anxiety, insomnia, irritability, and, in severe cases, seizures and psychosis [1]. The syndrome of inappropriate antidiuretic hormone secretion (SIADH) has been associated with several psychotropic medications, including antidepressants and antipsychotic medications [3]. The connection between BZDs and SIADH has not been extensively established in the scientific literature. Although the precise mechanism of ADH alteration by BZDs is unclear, the most plausible theory suggests central thirst dysregulation and vasopressin dysregulation via increased GABA activity [3]. In 1993, a link between BZDs and SIADH during withdrawal was noted in a single case report by Dr. Meagher [4], and benzodiazepine-induced SIADH was reported in a case study by Dr. Engel in 1988 [5].

Case report

An 85-year-old female with no previous history of cognitive or functional impairment was presented to the emergency department with a two-day history of recurrent episodes of blank stares, each lasting for several minutes and occurring multiple times a day. The episodes were followed by confusion and vivid visual hallucinations, where she reported seeing previously deceased individuals whom she had known. Her confusion included complete disorientation to time, person, and date, and she was unable to recognize her family members. As per collateral history, she was previously autonomous and independent for her basic and instrumental activities of daily living. Her medical history included hypertension, hypothyroidism and basal cell carcinoma with excision. Her medications included amlodipine 5 mg daily, levothyroxine 75 mcg daily, and clonazepam 1 mg as needed.

Upon arrival, the patient was vitally stable except for being hypertensive, with a blood pressure of 173/86 mmHg. The initial laboratory findings were remarkable for hyponatremia (Table 1). An infectious workup was done with negative result (Table 2). An abdominal imaging showed no fecaloma, and the patient was initially treated for hypoosmolar euvolemic hyponatremia due to possible underlying SIADH with 100 ml of 3% saline and 2 mcg of intravenous desmopressin. Despite the correction of her sodium levels, no cognitive improvement occurred. Subsequently, a neurological exam was performed and was entirely normal except for the altered mental status. The team proceeded with a cerebrovascular accident and encephalitis workup,

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Table 1. Laboratory Findings

Laboratory Findings	Values at the time of admission	Normal Range
Urea	6.8	3.0–8.0 mmol/l
Serum sodium	121	134–144 mmol/l
Serum osmolality	262	280–300 mOsm/kg
Urine sodium	<20	~20 mmol/l
Urine osmolality	393	50–1200 mOsm/kg
Thyroid-Stimulating Hormone (TSH)	2.49	0.40–4.50 mU/l
Vitamin B12	525	140–700 pmol/l
Serum cortisol at 8 am	585	140–690 nmol/l
Glucose	6	3.9–7.7 mmol/l
Bilirubin	9	3–17 umol/l
Alanine transaminase (ALT)	23	5–40 U/l
Alkaline phosphatase (ALP)	99	35–145 U/l

Table 2. Infectious work up

Microbiology Test	Result	Normal Range
Blood culture	Negative	Negative/Positive
Urine culture	Negative	Negative/Positive
Respiratory virus multiplex polymerase chain reaction (PCR)	Negative	Negative/Positive
SARS-CoV-2	Negative	Negative/Positive

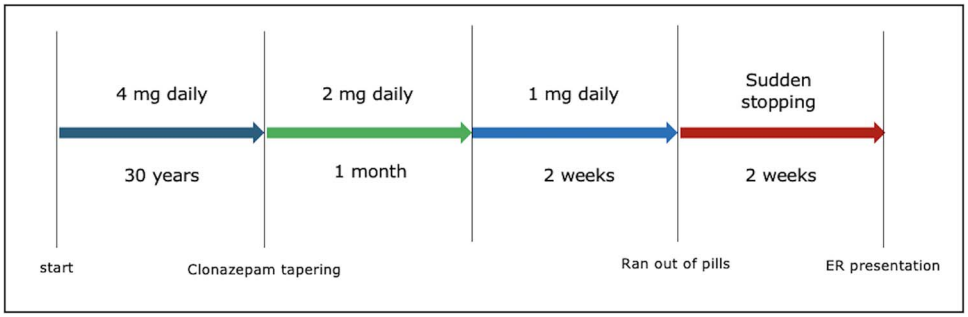

Figure 1. Timeline of the patient's clonazepam dosage changes.

performing both computed tomography angiography (CTA) and magnetic resonance imaging (MRI) of the brain. Neither of which showed evidence of acute stroke or signs of encephalitis.

Later, a review of the patient's psychiatric history and medication with the pharmacy revealed an undocumented anxiety disorder, managed by her family physician. Contrary to the prescription instructions, the patient had been taking 4 mg of clonazepam daily for 30 years instead of taking it as needed. She recently began tapering her medication as per her family physician, reducing the dosage from 4 mg daily to 2 mg daily for one month and then to 1 mg daily for another month. However, she ran out of medication two weeks before visiting the emergency department and did not obtain a refill (Figure 1). The clinical suspicion of a mixed delirium and SIADH due to long-acting benzodiazepine withdrawal was raised. On the second day of admission, and despite the ongoing symptoms of delirium, a trial of oral lorazepam 2 mg twice daily was initiated, equivalent to her usual 1 mg daily dose of clonazepam. On day three of her admission, the patient's confusion improved, and she no longer experienced visual hallucinations. The sodium level spontaneously was normalized to 135 mmol/l. As a result, the patient was discharged from the hospital with complete recovery and returned to her baseline cognitive state with future follow-up appointments to monitor her sodium level and lorazepam tapering plan.

Discussion

The prevalence of BZD use is increasing, particularly in the geriatric population [6]. Besides, the abrupt cessation or rapid tapering of BZDs often precipitates intense withdrawal symptoms, especially in the geriatric population. Pharmacokinetic and pharmacodynamic alterations in elderly females reduce the safety of BZD usage, making the treatment of withdrawal potentially challenging [7, 8].

Our case involved an elderly female patient who experienced BZD withdrawal from long-term clonazepam therapy. Nonconvulsive status epilepticus was considered in the differential diagnosis of confusion in the report. However, an electroencephalogram (EEG) and lumber puncture were not performed during the delirium to document any epileptiform changes, and this is a noted limitation in our report. Additionally, the association between BZD and SIADH withdrawal has been previously reported in a single case study specifically linked to lorazepam withdrawal. Thirty years after presenting the first case report that identified SIADH

as a symptom of BZD withdrawal [4], we present a second case in which SIADH was caused by clonazepam withdrawal. In this case report, the patient's symptom resolution was likely due to multiple factors, including sodium normalization and benzodiazepine reintroduction. A retrospective evaluation was conducted using the World Health Organization-Uppsala Monitoring Centre (WHO-UMC) [9] causality categories for drug withdrawal to assess the relationship between clonazepam withdrawal and hyponatremia and delirium. The assessment determined a probable causality and indicated that the reactions were likely due to clonazepam withdrawal rather than other drugs or conditions. This conclusion was supported by a positive rechallenge test, where reintroducing lorazepam resolved the hyponatremia and delirium. In the end, we emphasize adherence to the Journal of the American Society of Nephrology guidelines for the treatment of hyponatremia in the setting of SIADH, including the treatment of the underlying cause, initial therapy to raise the sodium level depending on the severity and chronicity [10]. Additionally, we recommend following the American Family Physician guidelines for benzodiazepine tapering and withdrawal management [8].

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Conflict of interest

The authors declare that there are no conflicts of interest in this study.

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Ethical approval

Not applicable.

Consent

Written informed consent was obtained from the patient for publication of this case report. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Guarantor

Dr Ahmad Alenezi.

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