Methazolamide-Induced Delirium

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A 74-year-old man became delirious 2 days after beginning oral therapy with methazolamide. The delirium was manifested by intermittent psychosis, incontinence of bowel and bladder, lethargy, and disorientation. These symptoms continued for 25 days despite many changes in his drug regimen, and complete laboratory, urologic, and neurologic work-ups. The symptoms resolved completely within 1 week of discontinuing methazolamide. This is the first case reported of delirium associated with methazolamide not accompanied by a metabolic imbalance.

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Carbonic anhydrase inhibitors (CAIs) commonly cause metabolic, hematologic, and gastrointestinal side effects. Sedation and dizziness are the common central nervous system (CNS) side effects, but serious CNS side effects are rare. A MEDLINE search dating back to 1966 revealed only one case of delirium associated with CAIs, and the association in that patient was obscured by the presence of a metabolic acidosis. Searches of the EMBASE and IPA data bases revealed no additional cases of delirium associated with methazolamide.

A patient became delirious after beginning methazolamide in the absence of any metabolic imbalances. Delirium persisted for weeks, and resolved promptly with discontinuation of the drug.

Case Report

An alert and oriented 74-year-old man was admitted to the hospital because of homicidal behavior and paranoia. He reported anxiety, difficulty concentrating, sadness, weight loss, and insomnia of 1-month duration. The patient was taking timolol 1 drop in each eye twice/day for glaucoma, and lorazepam 0.5 mg every morning and 1 mg at bedtime for anxiety. The following laboratory tests resulted in no clinically significant results: urine drug screen, urinalysis, SMAC-7 (glucose, serum creatinine, blood urea nitrogen, sodium, potassium, chloride, carbon dioxide), complete blood cell count, liver and thyroid function tests, RPR (rapid plasma reagin), and vitamin B12 and folate levels. The differential diagnosis was major depression with psychotic features or brief reactive psychosis.

The patient's outpatient drug regimen was continued, and on day 3 haloperidol was begun. The dosage was gradually increased to 15 mg/day during the first 4 weeks of hospitalization to control symptoms of paranoia and irritability. During this time, lorazepam was decreased to 1 mg at bedtime; pilocarpine 2% 1 drop in each eye 4 times/day and metipranolol 0.3% 1 drop in each eye twice/day were added to control intraocular pressure, and timolol was discontinued. The patient continued to be suspicious, irritable, and paranoid, but remained alert and oriented. He denied insomnia, anorexia, or anxiety. Haloperidol decanoate 75 mg was administered intramuscularly on day 29.

During week 5, sertraline 50 mg/day was begun, and haloperidol was decreased to 5 mg/day. Methazolamide 50 mg orally twice/day was added for better control of intraocular pressure. Two days after beginning methazolamide the patient became drowsy and confused.

During the next week his confusion progressed to a delirium state, and he became incontinent of bowel and bladder. Haloperidol was discontinued and a 3-day course of amantadine 100 mg orally...
twice/day was begun as the patient was having pseudoparkinsonian symptoms. During this time, sertraline was increased to 100 mg/day, and hydrochlorothiazide 12.5 mg/day and potassium chloride 10 mEq/day were started for mild hypertension and to prevent hypokalemia, respectively. Two weeks later sertraline was decreased to 50 mg/day and lorazepam was decreased to 0.5 mg at bedtime. At the same time, pilocarpine was increased to 4%, and haloperidol 1 mg orally at bedtime was begun.

The patient remained incontinent despite changes in his drug regimen, and on day 64 oral prazosin 1 mg twice/day and trimethoprim-sulfamethoxazole (TMP-SMX) 2 tablets twice/day were started subsequent to urologic work-up. Neurologic and laboratory work-ups completed during this time revealed no abnormalities. Over the next weeks the patient remained lethargic, sedated, disoriented, intermittently psychotic, and incontinent of bowel and bladder.

During week 9, methazolamide was discontinued. The patient regained control of bowel and bladder within a few days. His cognition improved remarkably, achieving baseline status 1 week after methazolamide was begun, and urinary and bowel incontinence became manifest 4 days later. Despite several drug changes and full urologic and neurologic work-ups, these symptoms persisted for 25 days with no identifiable etiology. The delirium cleared within 1 week of discontinuing methazolamide.

Several factors may confound a clear causal relationship. The patient received amantadine 100 mg orally twice/day for a total of 6 doses. Symptoms of delirium were noted the day after amantadine was started, but persisted with no change in severity for 20 days after it was discontinued. Although the dosage was

Discussion

To our knowledge, this is the only reported case of delirium associated with a CAI that was not accompanied by metabolic imbalance. The temporal relationship between initiation of methazolamide and onset of delirium, and resolution of symptoms with discontinuation, strongly suggest cause and effect. Sedation, disorientation, and confusion occurred 2 days after methazolamide was begun, and urinary and bowel incontinence became manifest 4 days later. Despite several drug changes and full urologic and neurologic work-ups, these symptoms persisted for 25 days with no identifiable etiology. The delirium cleared within 1 week of discontinuing methazolamide.

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Figure 1. Each line on the horizontal axis represents 1 day of hospitalization. The shaded area represents the time during which delirium persisted. Each horizontal line signifies the indicated agent. The left vertical line indicates the day of beginning the drug, and the right vertical line the day the drug was discontinued.
excessive for a patient with decreased renal function (creatinine clearance 63 ml/min), had amantadine been the cause, the delirium would not be expected to persist for 3 weeks. Psychosis associated with nontoxic dosages of amantadine usually resolves within 4 days after drug discontinuation, whereas toxic psychosis resolves within 1 week.\textsuperscript{3}

This clinical picture may possibly be explained by benzodiazepine withdrawal. Major withdrawal symptoms may manifest as delirium or psychosis, most commonly with short-half-life benzodiazepines such as lorazepam.\textsuperscript{4} A conservative schedule would require gradual benzodiazepine tapering over 4 weeks.\textsuperscript{5} It is unlikely that our patient's delirium was a consequence of benzodiazepine withdrawal, as lorazepam was gradually tapered over 6 weeks, and the delirium symptoms did not resolve until 2 weeks after discontinuation.

Delirium from haloperidol is another possibility, but is also unlikely as disorientation and confusion did not occur during the initial titration phase. Also, antipsychotic-induced CNS side effects are most common in the elderly when the agents are taken in conjunction with anticholinergic agents.\textsuperscript{6}

This case is a reminder that drug-induced mental status changes can easily be mistaken for or confound the diagnosis of a primary psychiatric illness. Iatrogenic causes of psychiatric symptoms are not always apparent and may not become manifest during work-up. The presence of delirium in the elderly may manifest as anxious, depressive, manic, or psychotic symptoms that may be diagnosed mistakenly and treated as major psychiatric disorders. This is especially true in older patients, who are most vulnerable to CNS side effects of drugs. It is estimated that 30–50% of elderly patients develop delirium during hospitalization, more than twice the frequency in younger adults.\textsuperscript{7}

In this patient, negative urologic and neurologic work-ups led to the assumption that he was experiencing worsening psychotic symptoms associated with a psychotic depression or brief psychotic disorder. He was treated with additional psychotropic drugs that did not correct the delirium and may actually have confounded the picture. Plans were being made for the man to be transferred to a nursing home facility had his psychotic symptoms not cleared. Fortunately, he was diagnosed with a psychotic depression, stabilized with antipsychotic and antidepressant drugs, and discharged to his own home.

References