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Ziconotide-induced psychosis: A case report and literature review

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Abstract

Ziconotide is an intrathecally administered medication indicated for the treatment of severe chronic pain in patients who are intolerant of or refractory to other treatment options. A black box warning is included in the packaging and states ziconotide is contraindicated in patients with a preexisting history of psychosis. Patients taking ziconotide should be monitored for evidence of cognitive impairment, hallucinations, or changes in mood, and ziconotide should be discontinued if neurological or psychiatric signs and symptoms appear. We present a case of a 49-year-old white male with no previous neuropsychiatric history who received ziconotide for several years before he developed command auditory hallucinations within 24 hours of a dose increase. Upon admission to the emergency room, the patient's pain management physician was contacted and the ziconotide dose was decreased and eventually discontinued. Because of a continuation of symptoms, the patient was transferred from the emergency room to an acute care psychiatric hospital where he was started on risperidone 1 mg orally at bedtime. At discharge, the patient was noted to be in good behavioral control without any hallucinations. The patient was encouraged to follow up with his pain management physician to determine if ziconotide should be reconsidered.

Keywords: ziconotide, ziconotide psychosis, ziconotide delirium, psychosis

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Background

Chronic refractory pain is difficult to manage with commonly used analgesics such as opioids, non-steroidal anti-inflammatory drugs, or muscle relaxants. Intrathecally administered analgesics are a viable option to consider when treating chronic refractory pain.[1,2] Ziconotide is a unique intrathecally administered analgesic used in the management of chronic refractory pain. Several clinical trials have shown ziconotide to be efficacious in treating pain of various etiologies as monotherapy or as an adjunct.[3-6]

Ziconotide is a synthetic derivative of a polypeptide found in the venom of the marine snail, *Conus magnus*. It mediates its potent analgesic effect via selective blockade of N-type calcium channels located on neurons in the central nervous system.[7] Ziconotide has a boxed warning for causing severe neuropsychiatric adverse events; thus, it is contraindicated in patients with a history of psychosis or mental illness.[8] Because of the kinetics and small therapeutic window of ziconotide, adverse events are associated with the rate of titration as well as the actual dosage administered.[9] Ziconotide-associated neuropsychiatric events may be diagnosed as substance/medication-induced psychosis if hallucinations or delusions are present after ziconotide administration when a patient has no psychiatric history.[10] Substance/medication-induced psychosis is often self-limiting and resolves upon discontinuation of the offending agent. Management of

psychosis and/or agitation due to various substances such as amphetamines, cocaine, alcohol, and cannabinoids often require the use of antipsychotics and benzodiazepines.[11-13] The management of psychosis due to ziconotide is less clear and not well studied. Here, we present the case of a 49-year old male who experienced paranoia and auditory hallucinations after an increase in the dosage of ziconotide.

Case

The patient was a 49-year-old white American male who presented to the emergency department for racing thoughts, auditory hallucinations, and palpitations. The patient's past medical history was significant for hypertension, chronic back pain, and spinal fusion surgeries following a motor vehicle accident in August 2012. The patient's pain management regimen consisted of intrathecal ziconotide 14 mcg/d, oxycodone sustained-release 10 mg every 12 hours, and tramadol 50 mg 3 times a day as needed. It was noted that the patient had been receiving ziconotide for several years prior to admission. However, his pain management physician increased his ziconotide to 14 mcg/d the day before presenting to the emergency department because of increased pain. The ziconotide dose before the titration was not documented. No other medication changes occurred around the time of the patient's psychosis. On day 1 in the emergency department, the patient was increasingly agitated and was treated with lorazepam 2 mg intravenously 1 time and had to be placed in 4-point restraints. He required an additional dose of intravenous lorazepam 1 mg because of continued agitation, and the restraints were removed in less than 4 hours. A urine drug screen testing for amphetamines, barbiturates, benzodiazepines, cocaine, opiates, phencyclidine, and cannabis returned negative. The negative urine drug screen, a negative blood alcohol level, and denial of substance abuse history from the patient and his wife effectively ruled out substance-induced psychosis. The patient's pain management physician was consulted and the ziconotide dose was decreased from 14 mcg/d to 7 mcg/d. Psychiatry was consulted, and the psychiatrist noted the patient improved following the dose decrease of ziconotide but still exhibited pressured speech and an intense labile affect. During the day 2 evaluation, the patient did not remember his conversation with the psychiatrist from the previous day and still exhibited pressured speech. During the next 2 days of observation in the emergency department, the patient received multiple doses of oral quetiapine 50 mg, intramuscular haloperidol 5 mg, and intravenous/intramuscular lorazepam 1 mg.

Following 4 total days in the emergency department, the patient was transferred to an acute care inpatient psychiatric unit for further work-up. According to the patient's wife, following the increase in the ziconotide dose, the patient began experiencing auditory hallucinations instructing the patient to kill her. She reported the patient was paranoid and would run outside every 5 minutes stating, "The guys are going to pick me up, and the guys are going to save me." Per the patient and the patient's wife, the patient had no psychiatric history, and a review of the patient's prescription records concurred. Prior to the transfer, the patient's intrathecal pump was shut off and drained of ziconotide. During the patient's first day on the psychiatric unit, he denied auditory/visual hallucinations and paranoia but still presented with pressured and sometimes indecipherable speech. The patient scored a 28 on the mini-mental state examination, indicating normal cognition. The patient was started on risperidone 1 mg at bedtime, oxycodone sustained-release 10 mg every 12 hours, trazodone 50 mg at bedtime as needed for insomnia, and oxycodone immediate-release 5 mg every 8 hours as needed for severe pain. Tramadol and quetiapine were discontinued.

Throughout the next 5 days of the patient's hospitalization, the patient's speech improved drastically, and he only received 1 dose of oral lorazepam 2 mg for anxiety. It was noted that the patient was calm and cooperative on the unit and was not responding to internal stimuli. The patient's blood pressure was continually elevated, and he was started on metoprolol tartrate 25 mg orally every 12 hours. The patient reported severe pain on a daily basis, described as a 7 on the numeric rating scale. He required oxycodone immediate-release on a daily basis, but he did not need more than 1 dose per day. A lidocaine patch 5% daily was started on day 3 and applied every day of the patient's psychiatric hospitalization to help alleviate his pain. After a total of 6 days on the inpatient psychiatric unit, the patient's psychotic behavior resolved, and he was discharged home with his wife along with a prescription for risperidone 1 mg at bedtime.

Literature Search

A literature search was conducted through PubMed using the following keywords: *ziconotide* and *ziconotide psychosis*. Results written in English were included. The initial search used *ziconotide* and yielded 366 articles. Of the initial 366 articles, a subsequent search using *ziconotide psychosis* resulted in 4 articles, 2 of which were case reports detailing ziconotide-induced psychosis. An additional search using the keywords *ziconotide delirium* resulted in 3 articles yielding 1 more case report. One additional case report was found in the Rutgers University databases by searching *ziconotide psychosis*. A total of 4 case reports describing ziconotide psychosis and delirium were found.

Discussion

Neuropsychiatric adverse events including psychosis were prominent during clinical trials studying ziconotide. These adverse events precipitated the black box warning upon ziconotide's approval. The following were the most common central nervous system adverse effects observed: confusion (33%), memory impairment (22%), speech disorder (14%), aphasia (12%), thinking abnormally (8%), and amnesia (1%).[8] The incidence of psychiatric adverse events were: hallucinations (12%), paranoid reactions (3%), hostility (2%), delirium (2%), psychosis (1%), and manic reactions (0.4%). Ziconotide's pharmacology clearly affects other aspects of the central nervous system aside from pain pathways. A recent review[14] detailing the relationship between ziconotide's mechanism of action and its safety profile indicates that the neuropsychiatric adverse events may be due to the blockade of voltage gated calcium channels in the prefrontal and cerebral cortex. In addition, a link between voltage gated calcium channels and dopaminergic neurotransmission has been proposed to contribute to symptoms of psychosis.[14]

Ziconotide's manufacturer and pain experts recommend starting at a dose of no more than 2.4 mcg/d. The manufacturer recommends titrating by no more than 2.4 mcg/d no more than 2-3 times a week to a maximum dose of 19.2 mcg/d. An expert consensus recommended titrating by no more than 0.5 mcg/d no more than once a week due to concerns of neuropsychiatric adverse effects upon rapid titration.[8,15,16] A recent review[9] of ziconotide dosing strategies noted that in long-term studies, the mean dose after titration was between 7 to 14 mcg/d. The patient in this case had his dose increased to 14 mcg/d which is on the higher end of the dosing spectrum. As the dose increases it makes sense that there is increased risk of adverse effects. He also experienced psychiatric adverse events almost immediately after his titration. A rapid and large dose increase of ziconotide may have contributed to the patient's psychosis.

A pharmacokinetic study[17] of intrathecal ziconotide including 22 chronic pain patients showed a half-life that ranged from 2.9 to 6.5 hours with a median of 4.5 hours. Based on these values, it would be expected that ziconotide would be eliminated after 5 half-lives, which could be anywhere from 14.5 hours to 32.5 hours. Ziconotide is highly hydrophilic, when administered intrathecally, it primarily remains in the cerebrospinal fluid. Consequently, the clearance of ziconotide is approximately equal to the rate of cerebrospinal fluid turnover.[7] The mechanism of elimination may tie into the resolution of neuropsychiatric adverse events. The manufacturer states that the median time to reversal of cognitive adverse effects ranges from 3 to 15 days.[8] The patient in this case showed improvement on the second day of the ziconotide taper. After discontinuing the ziconotide infusion and 10 days of hospitalization receiving antipsychotics and benzodiazepines, the patient's psychiatric symptoms resolved.

There are several published case reports[18-21] of ziconotide-induced psychosis and delirium. A case report by Phan and Waldfogel[18] described a similar case of ziconotide-induced psychosis of a 49-year-old woman who had a history of anxiety and depression. The patient presented with paranoia and auditory hallucination, which she started experiencing approximately 3 weeks prior to admission. Prior to admission, the patient was maintained on intrathecal ziconotide for approximately 3 months for complex regional pain syndrome due to a spinal injury and was receiving 4.9 mcg/d. There was no mention of a ziconotide dose change around the time that she was experiencing psychosis. The ziconotide was discontinued and the patient was treated with oral risperidone 0.5 mg nightly. This intervention resulted in clinical improvement. Whitlow et al[19] detailed a case report of ziconotide-induced psychosis of a 55-year-old woman who had a history of stage IV endometrial cancer, chronic obstructive pulmonary disease, gastritis, depression, and anxiety. She presented with confusion and paranoid delusions of family members poisoning her. The patient had been treated with ziconotide for the previous 7 months and her psychosis emerged after increasing the dose from 1.63 mcg/d to 2.53 mcg/d. The patient was started on oral paliperidone 6 mg daily and received paliperidone palmitate 234 intramuscularly on day 6. The medical team was unable to adjust the intrathecal pump, and the patient continued to experience paranoia and confusion throughout her 2-week admission.

Obafemi and Roth[20] described a case of ziconotide-induced delirium with psychotic features in a patient with a history of idiopathic small fiber peripheral neuropathy. Like other cases, the patient had his dose increased from 0.125 mcg/d to 1.5 mcg/d a week before admission. The patient was continued on his home medications of bupivacaine-dextrose 7 mL by epidural route continuously (7.5 mg/mL), fentanyl patch 100 mcg/h every 48 hours, desvenlafaxine 50 mg daily, alprazolam 2 mg daily, hydromorphone 4 mg orally every 4 hours as needed for pain, oxycodone immediate-release 15 mg every 6 hours as needed for pain, and tizanidine 4 mg every 6 hours as needed for muscle spasms. He was receiving an antidepressant and a benzodiazepine at home, indicating a psychiatric history. His ziconotide dose was gradually decreased from 1.5 mcg/d to 0.0353 mcg/d over 6 days and his symptoms were resolved by day 10. After discharge the patient returned to his pain management clinic complaining of increased pain and his ziconotide was re-titrated to 1.5 mcg/d over 2 weeks. His symptoms of hallucinations and confusion returned, which lead to the discontinuation of ziconotide. The ziconotide was replaced with intrathecal hydromorphone. This case shows that rechallenging patients

who experience neuropsychiatric adverse effects with ziconotide can result in the same response. Rechallenging can be considered, but the patient and prescriber should be aware of the risk of recurring symptoms and whether the benefit is worth that risk.

In a case by Levin et al,[21] a 38-year-old man with a known psychiatric history developed a case of intractable delirium while participating in a phase III trial of ziconotide. Before admission, his ziconotide infusion had been decreased from 0.65 mcg/h to 0.6 mcg/h because of worsening anxiety. His delirium was refractory to high doses of intravenous haloperidol, lorazepam, and midazolam. He was admitted to the intensive care unit and was subsequently intubated and paralyzed. His ziconotide pump was turned off, but the patient was still not responding to high doses of antipsychotics and benzodiazepines. He was ultimately treated successfully with electroconvulsive therapy.

The case presented here is the first published case report to document ziconotide-induced psychosis in a patient with no psychiatric history. Two clinical trials[4,6] did not exclude patients with a psychiatric history. A phase II clinical trial conducted by Wallace et al[6] found that 8 out of 18 patients in the extension phase discontinued treatment because of intolerable adverse effects, especially central nervous system adverse effects. One patient experienced hallucinations that lasted 57 days. A phase III clinical trial conducted by Rauck et al[4] found that central nervous system adverse effects such as dizziness, asthenia, somnolence, confusion, and ataxia were common, but there were no reports of psychosis in the ziconotide group. The incidence of neuropsychiatric adverse effects in patients without a psychiatric history is not known. However, this case report and safety data from clinical trials show that ziconotide certainly poses a risk of causing neuropsychiatric adverse events in patients without a psychiatric history.

Studies[22,23] show that severe pain and back pain is associated with psychosis. In addition, several case reports[24,25] have documented that opiate withdrawal can precipitate psychosis. In this case, severe pain may have contributed to psychosis, but the timing of ziconotide titration and psychosis onset leads us to believe that ziconotide was primarily responsible for causing psychosis. Psychosis due to opiate withdrawal appears unlikely because the patient did not exhibit symptoms of opiate withdrawal and was compliant with his prescribed opiate medications.

Conclusion

This case demonstrates that in patients who experience presumed ziconotide-induced psychosis, the discontinuation of ziconotide and administration of antipsychotics and benzodiazepines leads to positive outcomes. While concomitant use of tramadol may have contributed to the patient's psychosis, the patient's ziconotide was titrated the day before he presented with psychotic symptoms, making ziconotide the most likely causative agent. Like any other medication/substance-induced psychosis, the discontinuation of the offending agent seems like a logical approach. The patient was discharged with a prescription for risperidone, but it was not expected to be continued indefinitely. The patient was expected to require risperidone for only a short period of time. This case and other case reports support the fact that the neuropsychiatric adverse events of ziconotide are dose-related. Titration of ziconotide should be done slowly, but even if titrated correctly, neuropsychiatric adverse events may still occur. In light of intolerance of ziconotide, other modalities of pain management, such as intrathecal opiates, should be considered. Health care providers should be familiar with the care needed to resolve neuropsychiatric adverse events including the discontinuation of ziconotide as well as antipsychotics and benzodiazepines to alleviate psychosis and/or agitation.

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