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Possible hydromorphone-induced neurotoxicity in patients undergoing buprenorphine induction for opioid use disorder

Patients who are prescribed high doses of hydromorphone when being treating for opioid use disorder should be carefully monitored for signs of neurotoxicity.

ABSTRACT: Opioid-induced neurotoxicity is a constellation of neuropsychiatric signs, including delirium, myoclonus, hyperalgesia, and disorientation, that are thought to be attributable to the accumulation of metabolites from opioids. It is most commonly described in palliative patients. To date, opioid-induced neurotoxicity has not been described in the use of hydromorphone in buprenorphine/naloxone inductions. We reviewed charts of three patients who presented with possible opioid-induced neurotoxicity after receiving high-dose hydromorphone to manage opioid withdrawal during rapid low-dose buprenorphine/naloxone inductions. The patients received a maximum daily dose of 96 to 108 mg of oral hydromorphone. Prominent signs of opioid-induced neurotoxicity included disorientation and delirium, involuntary muscle contraction, slowed movement, and speech difficulties. All patients exhibited these signs within 1 to 3 days of hydromorphone use and stopped exhibiting these signs within 2 to 4 days of its discontinuation. Because high doses of hydromorphone are increasingly used with buprenorphine/naloxone inductions, it is important to recognize possible complications associated with its use.

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The ongoing opioid overdose epidemic in North America presents a pressing need for effective tools in managing opioid use disorder and preventing toxic opioid poisoning. In Canada, 7902 deaths in 2021 were due to apparent opioid overdose, a 23% increase from 2020 and a 113% increase from 2019.[1] Opioid agonist therapy effectively reduces the risk of all-cause and overdose deaths due to opioid dependence.[2] Buprenorphine/naloxone (Suboxone) is a first-line opioid agonist therapy option; its use results in displacement of any existing opioids in the system from their corresponding opioid receptors.[3] Standard guidelines suggest that patients avoid using opioids prior to buprenorphine/naloxone induction until they are in moderate withdrawal to avoid precipitating withdrawal.[4]

The rapid rise in the potency of unregulated opioids, including the increasing availability of toxic fentanyl analogues, has introduced new challenges to buprenorphine/naloxone initiation and the avoidance of precipitated withdrawal.[5] Consequently, new protocols suggest using inductions in which low and increasing doses of buprenorphine are administered without a period of abstinence (sometimes referred to as "microdosing" or "microinduction"), typically overlapping with administration of full agonists until receptors are saturated with buprenorphine.[6,7] One such agonist is hydromorphone. Published induction protocols use maximum total daily oral hydromorphone doses of 24 to 72 mg in buprenorphine induction.[8] Hydromorphone has become more widely used due to its own high receptor affinity; local provincial guidance during the COVID-19 pandemic suggested its use as a safer prescribed alternative to the toxic unregulated opioid supply in British Columbia.[9]

As potency of unregulated opioids increases, higher doses of prescribed opioids may be required to facilitate buprenorphine induction. This has been the case at the Creekside Withdrawal Management Centre, a medical withdrawal management facility in Surrey. In 2020, patients who were administered rapid induction with hydromorphone used as a bridging agonist experienced previously undocumented signs such as delirium and myoclonus; they were thought to be due to opioid-induced neurotoxicity, which was initially described in palliative care literature.[10,11] We present case reports for three patients with possible opioid-induced neurotoxicity.

Case data

All three patients were male, in their 20s or 30s. They were admitted to Creekside Withdrawal Management Centre for 7 to 9 days of treatment. All patients received oral hydromorphone (maximum total oral daily dose: 96 to 106 mg) for withdrawal management, and all received buprenorphine/naloxone via low-dose induction [Table]. Prominent signs of opioid-induced neurotoxicity included myoclonus/tremor/dystonia, dysarthria/delayed/slowed/paucity of speech, disorientation/delirium, and bradykinesia/difficult movement. All patients experienced these signs within 1 to 3 days of hydromorphone initiation and had resolution within 2 to 4 days of its discontinuation. Other medications administered included trazodone, quetiapine, and lorazepam.

Full review and approval of this study were provided by the Fraser Health Research Ethics Board. Given the potential benefits of reporting this information and the efforts made to protect the patients' identity, no express consent was obtained from the patients.

Patient 1

This patient was using 0.5 to 1.0 g of IV opioids daily, with sporadic use of stimulants and alcohol. On admission, his urine tested positive for fentanyl, morphine, benzodiazepines, and amphetamines. A 4-day buprenorphine rapid induction was started, with a day 1 total dose of 12 mg, 88 mg of hydromorphone, and trazodone, acetaminophen, and ibuprofen. On day 2, he received a total of 4 mg of buprenorphine and 96 mg of hydromorphone. On day 3, he was drowsy and disoriented and had visual hallucinations. Only 32 mg of hydromorphone was administered, with 8 mg of buprenorphine. On day 4, he denied having hallucinations but had slowed movements and was seen pinching at the air. Hydromorphone was discontinued, and the patient received 12 mg of buprenorphine. On day 5, he had difficulty making purposeful movements and had latent motor and verbal responses; he received 12 mg of buprenorphine. The slowing of his motor movements continued on day 6, and he received 16 mg of buprenorphine. On day 7, he was sent to the emergency department, with Emergency Health Services noting "twitching." A CT scan of his head was negative for acute pathology, and the patient received 14 mg of buprenorphine. By day 9, he was at baseline and was discharged on a buprenorphine dose of 12 mg daily.

Patient 2

This patient had a recent history of smoking 1 g of fentanyl daily and a prior period of abstinence while taking buprenorphine. On day 1 of induction, he received a total dose of 36 mg of hydromorphone and 1.5 mg of buprenorphine. On day 2, he presented with diaphoresis, nausea, and tremors; a total of 100 mg of hydromorphone was administered in scheduled doses to manage withdrawal, along with 0.5 mg of buprenorphine. On day 3, in addition to diaphoresis, the patient developed piloerection, chills, restlessness, and tremors. He had a total of 92 mg of hydromorphone and 2 mg buprenorphine. By day 4, he reported cognitive "fog" with speech latency and was described as "drooling" and "mute." Scheduled hydromorphone was discontinued, and the patient received only 36 mg of hydromorphone, along with 6 mg of buprenorphine. On day 5, he received a total of 16 mg of buprenorphine and was noted to have a vacant stare and reduced speech volume, rate, and tone. He was sent to hospital.

On day 6, the patient was no longer confused. Bloodwork, a lumbar puncture, blood cultures, and a CT scan of his head were

TABLE. Timeline of opioid-induced neurotoxicity signs and medication doses.

	No. patients treated	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9
NEUROTOXICITY SIGNS										
Myoclonus/tremor/dystonia	3	0	1	1	0	1	1	1	0	0
Dysarthria/delayed/slowed/paucity of speech	3	0	0	0	2	3	0	0	0	0
Disorientation/delirium	3	0	0	1	2	1	0	0	0	0
Bradykinesia/difficult movement	3	0	0	0	2	3	1	0	0	0
Hallucinations	1	0	0	1	0	0	0	0	0	0
MEDICATION AND AVERAGE DAILY DOSE (MG)										
Hydromorphone	3	57.3	101.3	45.3	36.0	0	0	0	0	0
Buprenorphine	3	1.7	4.8	9.0	10.0	14.7	16.0	15.3	20.0	12.0
Trazodone	2	100	100	0	0	0	0	0	0	0
Lorazepam	2	0	0	0	2	0	1	0	0	0
Quetiapine	1	0	50	50	0	0	0	0	0	0

Three patients were admitted to Creekside Withdrawal Management Centre for between 7 and 9 days of treatment and received a maximum dose of 96 to 106 mg of oral hydromorphone. Signs of opioid-induced neurotoxicity presented within 1 to 3 days of hydromorphone initiation and resolved within 2 to 4 days of its discontinuation.

Shading represents a scale from zero to the maximum value for each row.

normal. He continued to have muscle rigidity with blunted affect and facial and tongue fasciculations. Buprenorphine was withheld. The patient was given a one-time dose of 1 mg of lorazepam for possible dystonia and was started on antibiotics and an antiviral. On day 7, he was feeling well and received 12 mg of buprenorphine. By day 8, all cultures were still negative, and the patient was discharged. He was later titrated up to 24 mg of buprenorphine as an outpatient.

Patient 3

This patient had a recent history of using 3.5 g of IV fentanyl daily. On admission, he reported last using fentanyl 2 days prior and had used 30 mg of methadone each of the previous 2 days to manage his withdrawal. On admission, his urine tested positive for opioids, fentanyl, methadone metabolites, and benzodiazepines, and he appeared to be in withdrawal. He was provided a total of 48 mg of hydromorphone and was initiated on a 3-day rapid buprenorphine induction, with a total of 1.5 mg on day 1. On day 2, he was administered a total of 108 mg of hydromorphone, along with trazodone and 5.5 mg of buprenorphine. On day 3, he received a total of 12 mg of hydromorphone and 17 mg of buprenorphine. On day 4, he was disoriented and had latent responses and rigid movements, and his heart rate was 111. Hydromorphone was discontinued.

The patient was sent to the emergency department, where he was found to be slow-moving and speaking incomprehensibly, at times aphasic. A CT of his head was normal, and he was administered olanzapine. He was discharged from the emergency department back to the Creekside Withdrawal Management Centre, and his speech was normal after he received a total of 12 mg of buprenorphine. On day 5, he was still disoriented regarding time, was drowsy, and had slow, whispered speech and a slow gait. His symptoms resolved by day 6, and he was discharged on day 8 on a stable dose of 20 mg of buprenorphine.

Discussion

Hydromorphone and other opioids are increasingly employed in the management of opioid use disorder, including the management of withdrawal while patients initiate buprenorphine.[12] In the cases presented, we observed signs of unusual movement (myoclonus/tremor/dystonia), slowed movement (bradykinesia/difficult movement), difficult speech (dysarthria/delayed/slowed/paucity of speech), hallucinations, and disorientation/delirium. To our knowledge, these are the first reported cases of possible opioid-induced neurotoxicity in the management of opioid use disorder.

Prior reports of opioid-induced neurotoxicity were primarily in the palliative setting, outside the context of substance use disorders. The cases we have presented suggest that cautious monitoring may be necessary when prescribing high doses of hydromorphone as part of a management strategy for opioid use disorder in an inpatient setting, where doses are scheduled and neurotoxic metabolites may accumulate in the system. In addition, although no cases have been reported of opioid-induced neurotoxicity in the outpatient setting, it may be worthwhile assessing whether its symptoms occur when hydromorphone is prescribed to outpatients as an alternative to toxic supply.

Furthermore, the complexity of an unregulated drug supply with unknown adulterants makes interpreting these patients' presentations challenging. In our geographical area, opioids have been increasingly contaminated with benzodiazepines, and we have seen several cases of clearly defined opioid and benzodiazepine withdrawal that have responded to benzodiazepine administration. We considered benzodiazepine withdrawal as a diagnosis for these patients; however, they had atypical presentations without traditional signs and did not improve appreciably with benzodiazepine administration. Nonetheless, benzodiazepine withdrawal may be a contributor to what we observed.

Summary

We recognize the rapidly emerging need to expand available options for managing opioid use disorder and hope that the case reports presented allow clinicians to recognize possible adverse effects of prescribing in certain populations and to adjust management to ensure patient safety and retention. Because we adjusted our own practices to reduce the use of high-dose hydromorphone at the first sign of opioid-induced neurotoxicity symptoms, further cases have not occurred.

Competing interests

None declared.

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