Letters

Clonidine for the Management of Refractory Distressing Hallucinations, a Case Report

Dear Editor:

Clonidine is an antihypertensive agent frequently used for alternative purposes, including drug withdrawal, neuropathic pain, anxiolysis, and treatment of emergent agitation post-anesthesia.[1–4] Unlike traditional treatments for agitation or hallucinations such as antipsychotics, clonidine has no activity on dopaminergic, serotonergic, or gamma-aminobutyric acid receptors in the central nervous system; its activity is mediated via agonism of the alpha-2 adrenoreceptor.[4,5] The alpha-2 adrenoreceptor is implicated in promotion of natural sleep, decrease in delirium, anxiolysis, and neuropathic analgesia.[6–8]

There is minimal literature to the use of clonidine in palliative medicine. Most of the literature involves the treatment of neuropathic pain, autonomic dysregulation in pediatric populations, and spasticity.[1–5] There are no published reports for the use of clonidine for the management of hallucinations or delirium in palliative medicine; however, its use in the anesthesia emergent setting is well established.[1,2] Given the role of alpha-2 receptor agonists in decreasing anxiety and delirium and emergence agitation, clonidine may have a potential role for the treatment of hallucinations in palliative care.

Case Description

A 72-year-old female with suspected metastatic cancer (presumed urothelial primary based on imaging) was admitted to hospital in 2019 under medical oncology for ongoing diagnostic procedures after suspicious outpatient computed tomography (CT) scan. She was referred to the palliative care service for assistance with pain management, associated with likely abdominal metastasis. She had been suffering from rapidly worsening pain, which was poorly controlled with oral morphine in the community setting. This was changed to the subcutaneous route in hospital with reasonable effect.

During palliative care review, the patient admitted to auditory hallucinations—phenomena that had begun at home and had been increasing in frequency over several weeks. During her hospital stay, these hallucinations expanded to include visual and tactile forms and became increasingly disturbing and violent, incorporating visual and auditory hallucinations of her family members suffering graphic physical violence.

The patient and her family reported that auditory hallucinations had begun before commencement of opioids. Nevertheless, neurotoxicity from morphine metabolites was considered, and an opioid rotation to hydromorphone was done, with maintenance of analgesia but with no effect on hallucinations. Drug chart review was performed, and potential offending medications were ceased, including pro re nata diazepam (charted for anxiolysis) and hyoscine butylbromide (charted for abdominal pain). The patient was counseled regarding possible past trauma and/or drug and alcohol use and offered psychological support. However, she declined this assistance and denied any prior personal experiences that might be contributory. She had no previous psychiatric diagnosis and had never experienced hallucinations before a month of this admission to hospital. Her medical history was significant only for migraine, with prior surgical history, including cholecystectomy and bilateral cataract replacement. She was a lifelong nonsmoker and teetotaller and did not take any regular medication before her diagnosis.

The patient herself remained cognitively well without any gross disturbance in consciousness or executive function. She had no history concerning for an underlying dementia with family reporting good cognitive function and had no Parkinsonian features.

A septic screen was performed, as was a noncontrast CT scan of her brain. Chest X-ray revealed a possible left middle lobe pneumonia. The noncontrast CT brain and blood work revealed no pathology. Vital sign observations remained normal. The treating team prescribed a course of intravenous antibiotics in response to the chest X-ray findings with no impact on her hallucinations.

Her hallucinations were primarily nocturnal and distressing not only to the patient but also to her

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family members. Throughout all episodes of hallucinations, the patient remained lucid, with no fluctuation in her level of consciousness or orientation.

After initially being admitted to a multiple patient bedroom, she was transferred to a single room to enable family to stay overnight and minimize distractions.

Unfortunately, despite all the aforementioned measures, her complex hallucinations continued to worsen.

She was commenced on neuroleptic therapy, with haloperidol at 1 mg twice a day subcutaneously for 48 hours. This was ineffective, with no reported or observational difference to her symptoms. Levomepromazine was then trialed at 12.5 mg subcutaneously nocte for 24 hours; this was sedating but similarly ineffective in managing hallucinations. Olanzapine was then trialed at 5 mg nocte for 48 hours, proving less sedating than levomepromazine, but her hallucinations continued and were becoming more violent. Because of the minimal change with neuroleptics, and the sedation apparent with both levomepromazine and olanzapine, further treatment with these agents was not pursued.

At this stage, given three sequential neuroleptic agents had not provided relief from distress during a five-day trial but had resulted in daytime somnolence, multidisciplinary team discussions were held to determine a next course of action, with options considered including benzodiazepines for anxiolysis, antiepileptics for occult seizure activity, and alpha-2 agonism with clonidine.

It was decided to trial clonidine at night to assist with hallucinations and sleep because of potential for activity at the locus coeruleus to decrease central catecholamines and improve prefrontal cortical activity. This was discussed with the patient and her husband, both of whom provided verbal consent. Clonidine was started as a nocte subcutaneous dose of 100 μg; antipsychotic therapy was withdrawn.

On review, the morning approximately 10 hours after first dose of clonidine, the patient felt very well with a complete cessation of disturbing hallucinations. Her family had remained with her overnight and concurred that she had experienced a restful night. Oncology teams and nursing staff involved in her care commented on the dramatic improvement in her status.

Clonidine was continued subcutaneously at the same dose for five days with no recurrence of disturbing symptoms. Ongoing discussions with the patient revealed she had been experiencing visual hallucinations that she described as nondistressing spiritual visitations for several weeks; these had continued to occur despite clonidine therapy. The violent and distressing auditory, visual, and tactile hallucinations did not return.

After five days of subcutaneous clonidine, it was converted to per oral dosing at 150 μg at night; efficacy was maintained.

Clonidine continued orally for 12 days until the patient's condition deteriorated, and the focus of care shifted toward end-of-life management. Clonidine was converted back to the subcutaneous route at 100 μg nocte. One dose was withheld by nursing staff because of increasing somnolence; violent and distressing hallucinations returned the next evening and again resolved once clonidine restarted. The patient died after 22 total days on clonidine and was free from distressing hallucinations, apart from the 24 hours after a single missed administration.

Comment

Clonidine can be delivered effectively and safely via subcutaneous injection and shows potential for use as a treatment for complex hallucinatory symptoms that are distressing and do not respond to neuroleptic therapy. It was selected for our patient after consideration of alternative options because of potential benefits in decreasing central nervous system catecholamines and improvement of behavioral changes because of activity on the prefrontal cortex.[5]

As clonidine has a half-life of up to 16 hours, once-daily dosing is practical, allowing for nocturnal delivery without causing around-the-clock sedation.[5] Clonidine could be used as a nocturnal sedative, especially in patients whose goals of care preclude 24-hour sedation to alleviate distress.

The patient in our case requested a minimum of fuss in investigating the root cause of her hallucinations, and thus, expansion of diagnostic procedures and input from other specialty teams were not possible. Noncontrast CT of the brain was done, but she refused contrast injection or magnetic resonance imaging scanning of her brain. There thus remains clinical uncertainty as to whether her hallucinations were a symptom of an otherwise subtle delirium or another organic cause such as cerebral metastasis. Her hallucinations were primarily associated with sleep, which raises the possibility of a hypnagogic phenomena; however, they did intermittently persist into the daylight hours when she was alert and wakeful, leaving it unclear the exact relationship between her sleep cycle and hallucinations.

The diagnosis of hallucinations in the context of palliative care is somewhat contentious, with the differential list, including medication toxicity, cerebral metastasis, electrolyte disturbances, and organ failure. There is additionally the potential for hallucinations

to be sensory phenomena that carry personal and spiritual meaning and that the pathologization of these phenomena may not always be appropriate.[9] However one views the symptom in an epistemological sense: our patient's hallucinations were complex, violent, and causing anguish and thus, like any other distressing symptom, required urgent palliation. In this case, clonidine proved effective rescue therapy for distressing hallucinations that had been refractory to conventional therapy.

Future research is needed to compare clonidine to benzodiazepines, antipsychotics, and other standards of care in the management of distressing hallucinations.

Benjamin Thomas, MBBS, MMed
Illawarra Shoalhaven Local Health District
University of Wollongong
Wollongong, New South Wales, Australia
E-mail: benjamin.thomas@health.nsw.gov.au

Judith Jacques, NP
Hilary Stiel, FRACP, FAChPM
Central Coast Local Health District
Gosford, New South Wales, Australia

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Home Intranasal Dexmedetomidine for Refractory Dystonia in Pediatric Palliative Care

Dear Editor:

We report on the use of intranasal (IN) dexmedetomidine at home as a safe and effective sedative option for an 18-month-old toddler with refractory dystonia in the context of a progressive epileptic encephalopathy.

Case Description

An 18-month-old baby girl was referred to the Pediatric Palliative Care Service for a comprehensive evaluation of intractable dystonia. She suffered from epileptic encephalopathy because of lissencephaly, in the context of an unknown underlying disease, and her crises were refractory to multiple pharmacological treatments, such as levetiracetam (10 mg/kg/day), sodium valproate (50 mg/kg/day), and phenobarbital (5 mg/kg/day). Both adrenocorticotropic hormone and vigabatrin had been administered during the first months of life without any improvement. She had undergone percutaneous gastrostomy placement and Nissen fundoplication for gastro-oesophageal reflux; nevertheless, she continued to display frequent unpredictable dystonic crises of variable duration (from few minutes to four hours) with whole-body arching, diaphoresis, and inconsolable crying, during which it was impossible to touch or hold her. This condition caused both the baby and her parents significant distress and severely affected their quality of life.

At the time of the hospital admission, the crises were treated with baclofen (1.8 mg/kg/day), gabapentin (24 mg/kg/day), lorazepam (0.05 mg/kg/dose), and tetrabenazine (7.5 mg/kg/day) without response. Assuming that the crises were caused or exacerbated by pain, the pediatric palliative care team empirically administered analgesic drugs (oral acetaminophen 15 mg/kg, oral ibuprofen 10 mg/kg, and IN fentanyl 2 mcg/kg, and oral morphine 0.3–0.4 mg/kg/dose) without significant improvement. The team also explored and ruled out any treatable cause of pain (gastro-oesophageal reflux, hip dislocation, fractures, constipation, and gallbladder and kidney stones). An