Key Words: haloperidol, pharyngeal, bipolar, sertraline, side-effect, zuclopenthixol

Antipsychotic-Induced Laryngeal Dystonia

By James Richard O'Neill, Clare Stephenson

ABSTRACT ~ *We present the case of a young gentleman with diagnoses of bipolar affective disorder, high body mass index, and obstructive sleep apnoea. He was commenced on zuclopenthixol due to an inadequate response to quetiapine, but this swiftly led to marked physical health deterioration including shortness of breath, back pain, tachycardia, tachypnoea, and hypoxia. He was urgently transferred to hospital where he required intubation and intensive care admission.*

AFTER excluding other causes, it was felt that commencing zuclopenthixol had induced laryngo-pharyngeal dystonia leading to upper airway compromise and severely impaired respiratory function. He progressively recovered after zuclopenthixol was stopped, and he was transferred back to the psychiatric hospital after eight days.

THIS case highlights the potential challenges in diagnosing this rare but potentially fatal reaction to antipsychotics. We review the available literature on other cases including a potential interaction between typical antipsychotics and serotonin-specific reuptake inhibitors. Psychiatrists and emergency physicians should be aware of this condition and be alert in considering the administration of anticholinergics, which could be a simple yet life-saving intervention. Psychopharmacology Bulletin. *2022;52(1):61–67.*

Case History

The patient is in his mid-twenties and of South-East Asian background, with a diagnosis of bipolar affective disorder (BPAD). He was morbidly obese with a body mass index of around 50 and an associated diagnosis of obstructive sleep apnoea (OSA). He was prescribed a Continuous Positive Air Pressure (CPAP) machine for this, but rarely utilised it. In addition, the patient suffered from hypertension, eczema, and gastro-oesophageal reflux disease. His regular medications included quetiapine, sertraline, amlodipine, loratadine, and omeprazole.

During inpatient psychiatric detention, it was felt that quetiapine was not sufficiently treating his bipolar symptoms, and haloperidol was deemed the most appropriate alternative which was cautiously initiated and titrated up. However, four weeks after commencing haloperidol, the patient complained of difficulty sleeping and having noisy breathing when laid on his side. There was evidence of stertorous breathing on examination, along with significant intraoral soft tissue.

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It was suspected that the haloperidol may have led to a change in the muscular tone of his upper respiratory system, causing a partial obstruction. Haloperidol was therefore switched back to quetiapine.

There was further deterioration in his presentation associated with verbal and physical hostility, and it was also suggested that he may be experiencing paranoid delusions and auditory hallucinations. A decision was made to add zuclopenthixol at 25 mg twice daily to his psychotropic regime.

Symptomatology

The patient received three doses of zuclopenthixol 25 mg over a 36-hour period before describing acute lower back pain. His heart rate was elevated at 128 beats per minute, but blood pressure (127/75 mmHg) and oxygen saturation (95%) was within range. He presented as clammy but denied any chest pain. Observations were repeated around forty minutes later, which showed worsening tachycardia (150 beats per minute), profound tachypnoea (45 breaths per minute), and a drop in oxygen saturation (90%). There was no fever, obtundation or stiffness, and neuroleptic malignant syndrome therefore appeared unlikely as a diagnosis. He was now reporting subjective shortness of breath and appeared objectively to be in respiratory distress. Oxygen was commenced and an ambulance was called. Electrocardiogram tracing showed sinus tachycardia with no evidence of cardiac ischaemia.

On arrival to the Emergency Department two hours after symptom onset, there was evidence of partial airway obstruction. His oxygen saturations were within range on room air, but his blood lactate levels were markedly elevated at 6.9 millimoles per litre (mmol/L). On examination, the chest was largely clear with mildly reduced air entry at both bases. A surgical opinion was sought due to abdominal pain and hyperlactataemia, but no clinical evidence of acute intra-abdominal pathology was evident on examination. Repeat blood gas measurements a few hours later showed rising lactate (14.1 mmol/L) and new metabolic acidaemia (pH 7.21, bicarbonate 14.4 mmol/L) with normal blood sugars. Cranial imaging was unremarkable, and computed tomography showed bibasal consolidation of the lungs.

Diagnosis & Treatment

Sepsis of unknown origin was suspected, so intravenous fluids, ceftriaxone and metronidazole were administered, and both urinary catheter and central line were inserted. He required intubation due to worsening respiratory distress and was admitted to the Intensive Care Unit (ICU).

Following intubation, oxygen saturations were well maintained; this was taken to suggest there was no lower respiratory compromise, and that this presentation was primarily due to upper airway compromise rather than any aspiration or pneumonia. Oral medications including zuclopenthixol continued to be administered via a nasogastric tube.

Creatine kinase was elevated at around 1800 units per litre (U/L), but D-dimer, procalcitonin, c-reactive protein, and troponin were all within range. Cultures of blood, urine and endo-tracheal secretions failed to identify any causative organisms. Piperacillin-and-tazobactam antibiotics and replacement fluids were given intravenously. The following day, plans were put in place to slowly wean ventilation and sedation. On waking, the patient was agitated secondary to hyperactive delirium, and was administered a dose of intramuscular haloperidol.

Later that night, a further deterioration was noted whilst on ICU with a recurrence of tachycardia and tachypnoea, and the patient was subsequently re-intubated. A review by ear, nose, and throat (ENT) specialists took place which found significant soft tissue deposit around the neck and tongue. It proved difficult to successfully perform naso-endoscopy, and formal assessment of the larynx was not possible. Dexamethasone was prescribed to reduce any oedema or swelling around the upper airway. Creatine kinase measurement was repeated due to darkened urine and had increased to 3200 U/L. Renal function was unimpaired.

The patient was successfully extubated after 48 hours, but soon after became unresponsive, developing extensor posturing and dilated pupils. Seizure activity was suspected, and lorazepam was given intravenously to good effect. Further ENT advice was sought due to persistent stridulous breathing, which was attributed to soft tissue collapse due to his large body habitus.

A diagnostic review discussed the link between acute onset of symptoms and starting zuclopenthixol, as well as the historical stertor observed with haloperidol. In the absence of any other suggested cause, it appeared increasingly likely that an idiosyncratic reaction following exposure to first-generation antipsychotics was the cause of his symptoms. Zuclopenthixol was ceased three days into his medical hospital admission.

The patient was more rousable and engaged in small conversation on the fifth day of hospital admission. During times of alertness, evidence of upper airway obstruction was not present, although speech and language therapists noted a mild stridor on review which the patient considered normal for himself.

The patient was discharged from the intensive care unit after six days and transferred to a general ward. Physiotherapy assessment detailed good movements while in bed, but persistent drowsiness

limited further assessment of sitting or standing. His mobility had improved the following day when re-reviewed, and he was able to walk with supervision. The patient continued to make an uneventful recovery, and after an eight-day hospital admission, he was discharged back to inpatient psychiatric care with a diagnosis of laryngo-pharyngeal dystonia secondary to zuclopenthixol, on the background of obstructive sleep apnoea.

Discussion

Dystonia is defined as an uncontrolled muscular spasm in any part of the body.[1] Muscular dystonias are commonly seen with antipsychotic use, especially when high-potency first-generation agents are used in young males with mood disorders.[1,2] Acute dystonia tends to manifest within the first three days of commencing a dopamine antagonist.[3] While acute dystonias of the laryngeal or pharyngeal muscles are less common, up to 30% of patients treated with neuroleptics can develop dystonia of some form.[4] On the whole, extrapyramidal side effects from psychotropics are often poorly recognised.[5]

It is suspected that D2-receptor blockade in the midbrain is attributable to the pathophysiology of antipsychotic-induced dystonia, especially when the caudate nucleus, putamen and globus pallidus are affected.[6] This would explain the inverse relationship between age and the likelihood of dystonia, as dopaminergic activity has been found to reduce globally with advancing age. Dystonia is typically not a life-threatening condition, but laryngospasm is considered an exception due to the potential for upper airway compromise.

Acute laryngeal dystonia was first diagnosed in 1978 and is a rare but lethal form of dystonia,[7] which can cause sudden death through upper airway obstruction.[8,9] It is rarely considered as a diagnosis and is likely therefore underreported in incidence.[7,10,11] There is evidence that the reaction is independent of dosage, suggesting an idiosyncratic hypersensitivity reaction. Due to the rare and life-threatening nature of the condition, the evidence base available is largely rooted in case reports.[7] Cases are predominantly associated with first-generation agents,[1] but there are reports of similar presentations from a variety of different atypical antipsychotics also, including aripiprazole,[12] ziprasidone,[13–15] risperidone[9,16,17] and olanzapine.[18]

Presentations of upper airway obstruction were apparent universally across documented acute laryngeal dystonia cases, but the specific manifestation of this varied between dysphonia,[4,17,19–21] choking, respiratory distress,[9] stridor and desaturation.[22] Diagnosis is typically confirmed by a positive response to anticholinergic medication, the inability to

conduct forceful upper airway manoeuvres such as coughing or sniffing, or by observing limited vocal cord movement via laryngoscopic visualisation.[7]

Our literature search highlighted another similar case report of laryngeal dystonia in a young boy with no past medical history, who took chlorpromazine and fluoxetine in overdose.[19] Many factors are transferrable between this case and ours. Both involved young males taking typical antipsychotics alongside serotonin-specific reuptake inhibitors (SSRIs), and both cases developed symptom onset at around thirty-six hours following their initial dose. Interestingly, it was suggested in this historical case report that SSRI medication could have exacerbated the effects of the typical antipsychotic through inhibition of CYP450 hepatic enzymes.[23] There is currently no guidance in the British National Formulary that chlorpromazine and fluoxetine can act as potential interactants.[24] The role of sertraline interacting with first-generation antipsychotics in our case could therefore be investigated further as a potential contributory factor.

Anticholinergic medications are commonly administered for acute dystonias parenterally, and acute laryngeal dystonia can also be successfully treated in this manner.[7,10,25] They are believed to work through inhibition of nicotinic and muscarinic receptors within the striatum.[26] There is also evidence base for the use of antihistamines,[7,22] benzodiazepines,[27] and benztropine[10] in the therapeutic relief of dystonia.

During the acute phase of our case, laryngo-pharyngeal dystonia was not considered as a diagnosis. Means to confirm this were therefore not fully examined at the time, and naso-endoscopy was unsuccessful when attempted by ENT. However, evidence of upper airway compromise was noted which mirrors with other identified cases,[19,20,21,28] and given our patient meets many of the risk factors for dystonia detailed above, our diagnosis of acute laryngeal dystonia appears to be corroborated. Interestingly, no such reaction was observed in our patient when he was prescribed quetiapine or risperidone, but developed when switched to both haloperidol and zuclopenthixol, both first-generation agents.

The patient's apparent reaction to haloperidol earlier in the year could suggest a more universal reaction towards typical antipsychotics. This was corroborated by an exacerbation in clinical state after the patient was administered haloperidol for suspected delirium. The Maudsley guidelines recommend that with administration of haloperidol intramuscularly, anticholinergics should be pre-emptively prescribed in case of laryngeal dystonia.[1] Anticholinergics were not administered through our case, and the only medication that

could have directly acted therapeutically on dystonia throughout our case was lorazepam, which was incidentally given for suspected seizure activity three days into admission rather than to treat dystonia. However, it is worth noting that zuclopenthixol will have been steadily eliminated from his system over time whilst conservative measures were applied on ICU.

Increased alertness to the presence of dystonia in varying forms would lead to swifter consideration and prescription of therapeutic agents, which most likely would have expedited the patient's recovery. We would suggest that given the relatively low risk of anticholinergics versus the high risk of acute dystonia, a low threshold for use should be applied in the event of respiratory distress if the patient is receiving medications considered high risk. Repeated dosing of anticholinergics may be required to achieve the desired effects. ✤

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Consent Statement

Verbal consent was obtained from the patient in question on 23rd November 2021, which was witnessed and formally recorded.

Declarations of Interest

None.

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Author Contributions

James R. O'Neill – data compiling, literature review, completion of report.

Clare Stephenson – data compiling, literature review, completion of report.

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