

Acute laryngeal dystonia: drug-induced respiratory failure related to antipsychotic medications

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ABSTRACT

Acute laryngeal dystonia (ALD) is a drug-induced dystonic reaction that can lead to acute respiratory failure and is potentially life-threatening if unrecognized. It was first reported in 1978 when two individuals were noticed to develop difficulty breathing after administration of haloperidol. Multiple cases have since been reported with the use of first generation antipsychotics (FGAs) and more recently second-generation antipsychotics (SGAs). Acute dystonic reactions (ADRs) have an occurrence rate of 3%-10%, but may occur more frequently with high potency antipsychotics. Younger age and male sex appear to be the most common risk factors, although a variety of metabolic abnormalities and illnesses have also been associated with ALD as well. The diagnosis of ALD can go unrecognized as other causes of acute respiratory failure are often explored prior to ALD. The exact mechanism for ALD remains unclear, yet evidence has shown a strong correlation with extrapyramidal symptoms (EPS) and dopamine receptor blockade. Recognition and appropriate management of ALD can prevent significant morbidity and mortality.

Introduction

ALD is a life-threatening drug-induced dystonic reaction most commonly related to the administration of an antipsychotic medication. ALD is a type of acute dystonic reaction that occurs amongst other EPS characterized by laryngospasm leading to respiratory compromise that requires immediate medical attention. This phenomenon has been well described in medical literature, however the diagnosis is likely underreported. As such, this article will provide an overview of acute dystonia, specifically ALD, including epidemiology, risk factors, pathophysiology, clinical manifestations, diagnosis, management, and the medications associated with the occurrence of ALD.

A review of current literature was conducted using PubMed with the search terms "acute laryngeal dystonia", "acute respiratory failure", "laryngospasm", "acute dystonic reaction", "extrapyramidal symptoms", "first generation antipsychotics", "second generation antipsychotics", "dopamine", and "anticholinergics". All articles were reviewed for relevance and those not pertaining to ALD were excluded. Ultimately, 24 articles were used for this review. There are no randomized blinded clinical trials evaluating ALD.

Epidemiology

The prevalence of ADRs varies based on population, time frame, and medication. Occurrence of ADRs range from 3%-10%¹, however

analysis of pooled data has shown ADRs to be as high as 51.2% with high-potency antipsychotics². ADRs typically occur more frequently with FGAs compared to SGAs³. The first reported cases of ALD were described by Flaherty and Lahmeyer⁴ in 1978 when two individuals developed difficulty breathing shortly after initiating haloperidol. Since then, Christodoulou and Kalaitzi⁵ detailed 28 cases of ALD related to FGAs. Even fewer cases have been reported to be associated with SGAs^{1,6-12}. Despite being relatively uncommon, it can be life threatening with as many as four deaths due to ALD having been reported following administration of Haloperidol^{5,12}.

Risk Factors

While young males (under the age of 30 years) seem to be more commonly affected by ALD, 3 out of the 4 deaths related to ALD occurred in women^{5,12}. FGAs seem to carry the highest risk of ALD, specifically high potency neuroleptics (fluphenazine, haloperidol, and thiothixene), however low potency neuroleptics (chlorpromazine and thioridazine), SGAs, and metoclopramide have been implicated in several cases of ALD as well^{1,4,5,7-13}. There are mixed data on the effect of medication dosing in ALD. Cases of ALD have been reported with high doses of neuroleptics as well as low to moderate doses^{4,5,12,13}. Therefore, it was proposed that there may be an idiosyncratic hypersensitivity to neuroleptics that is associated with ALD and that hypersensitivity increases the risk of future occurrences of acute dystonia¹³. Intramuscular administration has also been described as a risk factor for ADRs¹⁴. Additional risk factors reported in the literature include: alcoholism, hyperthyroidism, hypoparathyroidism, hypocalcemia, dehydration, mononucleosis, AIDs, uremia, acute respiratory infection, and stress^{3,5,13,15,16}.

Pathophysiology

The exact mechanism of ADRs including ALD remains unknown. The most widely studied target of EPS has been dopamine, specifically the D2-receptor^{18,19}. Animal models using positron emission tomography (PET) have evaluated the occupancy of D2-receptors with haloperidol as a marker for antipsychotic effect and EPS occurrence. D2-receptor occupancy of 78% was shown to correlate with a high incidence of EPS. The EPS threshold was reached at relatively low drug levels (<5 mg/day) which means that EPS is essentially unavoidable when using FGAs¹⁸. Another theory proposed for the pathogenesis of ADRs is that there is a relative surge in dopaminergic activity related to an increase in dopamine synthesis and metabolic turnover that follows initial dopamine receptor blockade²⁰. The acute timing in which ADRs typically occur support this theory, however it wouldn't explain the occurrence of delayed dystonic reactions that have been reported. A genetic predisposition has been suggested in families with

a hereditary form of spasmodic dysphonia, specifically DYT4 dystonia, who present with prominent laryngeal or lingual dystonias. The gene of focus is a mutation in the TUBB4 gene²¹. While the TUBB4 gene has been shown to play a role in a specific form of dystonia, further genetic studies may provide insight into the occurrence of ALD in patients who may have a familial predisposition.

Medications

FGAs have classically been thought to produce EPS more frequently than SGAs owing to the higher affinity to dopamine receptors. This thought was based on studies comparing side effects of FGAs to clozapine, the initial SGA proven to be efficacious in the treatment of schizophrenia but with lower binding affinity to the D2-receptor and consequently lower incidence of ADR. The therapeutic activity of SGAs utilize serotonin receptor (5HT_{2A}) blockade more than the D2-receptor which was thought to be related to a decreased propensity to produce EPS²². Additionally, lower binding affinity and faster dissociation from D2-receptors by SGAs contributes to a decrease in the occurrence of EPS¹⁹. While clozapine provided a foundation for the therapeutic effect of SGAs and the perception that they would have a lower incidence of EPS, the development of newer SGAs show that the D2-receptor binding affinity is variable. In fact, more recent literature has described the D2-receptor blockade of SGAs such as aripiprazole, olanzapine, risperidone, and ziprasidone to have intermediate to high antagonistic D2 effect comparable to some FGAs (haloperidol, fluphenazine)²². The increased ability for SGAs to produce dopaminergic blockade with subsequent EPS has been observed in multiple case reports where SGAs were attributed to the occurrence of ALD. SGAs associated with ALD include aripiprazole, asenapine, olanzapine, risperidone, ziprasidone^{1,7,9,10,12,23}.

Clinical Manifestations

ADRs are characterized by sustained muscle contraction producing involuntary, abnormal postures, often in a twisting nature affecting the trunk, neck, face, and extremities^{2,17}. ALD can occur in association with other ADRs present in different areas of the body⁵. Symptoms typically occur shortly after administration of an antipsychotic. 50% of cases occur in the first 48 hours and up to 90% of cases occur within the first five days of starting or increasing the dose of an antipsychotic^{1,3}. Patients typically exhibit signs and symptoms of slurred speech, dysphagia, dysphonia, stridor, and dyspnea^{9,11}. Often times, patients clutch their throat as if to signify that they are in respiratory distress¹³. Consequently, patients may present with altered mental status and tachycardia if hypoxic¹⁰.

Diagnosis

Since the occurrence of ALD is rare, the diagnosis

may not initially be recognized^{7,12}. A recent history of administration or increase in dose of an antipsychotic should raise clinical suspicion of ALD. Additional etiologies including allergic reaction and airway obstruction should be ruled out when considering ALD. If the clinical context and presentation are consistent with ALD (clutching of the throat, worsening stridor, breathiness, slurred speech, dyspnea, dysphagia, and/or dystonias in other parts of the body), the diagnosis of ALD can be made in two different ways. First, if there is immediate response to parenteral anticholinergic therapy. Second, if there is an inability to perform glottic challenges including sniffing or forceful coughing. ALD can be confirmed via laryngoscopy showing abnormal motion of the vocal cords. Vocal cords will either have decreased movement or will have paradoxical motion (adduction with inhalation)¹⁰.

Management

There are two types of medications that effectively treat ALD, anticholinergics and antihistamines. The anticholinergic medications include biperiden, benztropine, trihexyphenidyl, and orphenadrine. Diphenhydramine is the most commonly used antihistaminic agent. The route of administration can be intramuscularly or intravenously and dosing usually consists of biperiden 2mg, benztropine 2mg, or diphenhydramine 25mg to 50mg². The reversal agents should be continued over the next several days as dystonic reactions are likely to recur even if the antipsychotic is discontinued^{2,15}. Multiple cases have shown resolution of symptoms of ALD with administration of anticholinergic or antihistaminic agents^{1,4,5,6,8,9,10,13}. In one case, there appeared to be utility in using benzodiazepines in ALD¹, however there is insufficient evidence to suggest routine use of benzodiazepines in ALD. A major concern with benzodiazepines is the risk of respiratory compromise. A case reported by Lanzaro et al. described the use of clozapine in treating ALD when initial management with anticholinergics and antihistamines were ineffective. The authors attributed the improvement in the dystonia to the antidystonic effect of clozapine²⁴. It should be noted that the patient in this case was also receiving FGAs for treatment of persistent psychosis in addition to the anticholinergic and antihistaminic agents. Therefore, it is likely that substituting the FGAs for an SGA such as clozapine, which has a low potential for causing EPS, may have been key to resolving ALD in this case.

Conclusion

While ALD remains a rare complication of antipsychotic drug administration, the awareness and ability to act quickly is critical in treating this life-threatening event. The incidence of ALD related to SGAs continues to be reported in literature, therefore ALD should remain as a differential diagnosis in all patients being treated with antipsychotics

regardless of the class. Clinicians who are managing patients being treated with antipsychotics and those evaluating patients in acute care settings such as urgent cares and emergency departments should be aware of the presenting signs and symptoms of ALD and the appropriate treatment in order to prevent future deaths from occurring.

As mentioned previously, there are limited available data in the published literature regarding ALD and the cited references and conclusions are based largely on case reports and case series. This represents a limitation of this review article as the conclusions of causality cannot be inferred from uncontrolled observational data. Therefore, it may be difficult to generalize to clinical practice, introduces the possibility of over-interpretation of results, and has the potential for confounding and recall bias within the study samples. However, due to the rare nature of this disease and high likelihood of under recognition, large scale observational studies are challenging and randomized clinical trials may not capture enough events to be statistically significant. Case control studies may provide a better understanding of incidence rates, allow for detection of delayed clinical outcomes and infer causality. Despite the limitations as previously described, the cumulative data thus far provides a narrative review of a unique phenomenon that requires a high degree of diagnostic suspicion that is important to recognize in the appropriate clinical setting due to the available treatments that may be life-saving.

Conflicts of Interest

There are no conflicts of interest or forms of financial support.

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