

Case Report

Angioedema with haloperidol: a case report*Angioedema com haloperidol: um relato de caso***Ana Lúcia R. Costa¹, Sabrina Jesus², Mónica Almeida³, João Alcaface⁴**

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ABSTRACT: Haloperidol is a first-generation antipsychotic and one of the most commonly used drugs within this category. It is a potent centrally acting antagonist of type 2 dopamine receptors, with low anti-alpha-1-adrenergic activity and no antihistaminic or anticholinergic activity, regularly used in cases of agitation. Angioedema is an especially serious side effect, characterized by marked edema of the subcutaneous or submucosal tissue, and can affect various parts of the body, and may even culminate, in the most severe cases, in death. It has already been described with the administration of several antipsychotics, such as clozapine, risperidone, ziprasidone, and chlorpromazine, but it is rare as a result of administration of haloperidol, occurring in <1% of cases. This article aims to describe the development of angioedema in a patient with acute confusional syndrome after the second administration of IM haloperidol for symptomatic control of agitation in an emergency department setting.

Keywords: Haloperidol; Angioedema; Side effects.

RESUMO: O haloperidol é um antipsicótico de primeira geração e um dos medicamentos mais usados dentro dessa categoria. É um potente antagonista de ação central dos recetores de dopamina tipo 2, com baixa atividade anti alfa 1 adrenérgica e sem atividade anti-histamínica ou anticolinérgica, regularmente utilizado em casos de agitação. O angioedema é um efeito colateral especialmente grave, caracterizado por edema acentuado do tecido subcutâneo ou submucoso, e pode afetar várias partes do corpo, podendo até culminar, nos casos mais graves, em morte. Já foi descrito com administração de vários antipsicóticos, como clozapina, risperidona, ziprazidona e clorpromazina, no entanto é raro como resultado da administração de haloperidol, ocorrendo em <1% dos casos. O objetivo deste artigo é descrever o desenvolvimento de angioedema em um paciente com síndrome confusional agudo após a segunda administração de haloperidol IM para controle sintomático da agitação em contexto de serviço de urgência.

Palavras-chave: Haloperidol; Angioedema; Efeitos adversos.

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INTRODUCTION

Haloperidol is a first-generation antipsychotics, also known as classic or typical, belonging to the butyrophenone family. It is a high potency drug and one of the most frequently used antipsychotic drugs in the world. It is a potent antagonist of central type 2 dopamine receptors, with low alpha 1 adrenergic antagonism, and has no antihistaminic or anticholinergic activity¹.

The most common side effects include extrapyramidal reactions induced by blockade of dopamine receptors and others, such as electrocardiographic changes or orthostatic hypotension, which are less frequent and result from blockade of alpha-adrenergic receptors. Angioedema is a very rare side effect, occurring in <1% of cases¹. The high potency and its low probability of interacting with non-dopaminergic receptors make this drug free from other side effects and, therefore, a first-line choice in the treatment of agitation.

This medication is widely used, with proven efficacy in improving symptoms of schizophrenia, treating manic episodes associated with bipolar affective disorder, persistent agitation, and aggression in patients with dementia or acute confusional syndrome, also called delirium. This neuropsychiatric disorder is a common cause of hospital admission in the elderly population and is characterized by disturbances of consciousness, attention, cognition, and perception, with an abrupt onset and fluctuating course, being relatively common during hospitalization. The incidence of an acute confusional state ranges from 6% to 56% in hospitalized patients and reaches almost 80% in intensive care units¹⁻⁴.

Although rare, angioedema is an especially serious and potentially fatal side effect. It is characterized by marked edema of the subcutaneous or submucosal tissue, increased capillary permeability, and plasma leakage, which can affect various parts of the body, including the face, mouth, and extremities. When drug-induced, it is believed to promote hypersensitivity-related immunoglobulin E (IgE)-caused edema⁵⁻⁷.

Angioedema has been reported as an adverse effect of several antipsychotics, such as clozapine, risperidone, ziprasidone, and chlorpromazine, however, it is rare as a result of haloperidol administration, with only 4 cases described in the literature⁸⁻¹⁰.

In 2012, Andrew J. Muzyk describes the first case of a 24-year-old man who starts treatment for schizophrenia with oral haloperidol and after 24 hours develops periorbital and lingual edema that improves with the administration of methylprednisolone. After 2 weeks, he returns to the emergency department with similar symptoms, caused by iloperidone, an atypical antipsychotic, belonging to the class of organic benzisoxazoles⁸.

In 2015, the case of a 47-year-old woman who was admitted to the emergency department due to agitation is

described. 10mg of haloperidol IM is administered, after 10 minutes she develops a condition characterized by edema and protrusion of the tongue with respiratory difficulty, which does not yield to pharmacological intervention, requiring tracheostomy⁶.

In 2017, 2 cases are described, an 11-year-old girl and a 27-year-old man, who developed facial and tongue edema, in the 1st case after 2 days of oral haloperidol administration of 1mg, and in the second case after 4 hours of treatment. administration of haloperidol 10mg IM^{11,12}.

The clinical case presented describes the development of angioedema in a patient with an acute confusional syndrome in which haloperidol is administered for symptomatic control.

CASE REPORT

The case presented describes a 77-year-old woman who was previously autonomous for activities of daily living. She has a personal history of obesity, stage IV chronic kidney disease, systemic arterial hypertension, non-insulin-dependent diabetes mellitus, and dysthymia. Usually medicated with sitagliptin 50mg daily, amlodipine/olmesartan 5/20mg daily, bisoprolol 5mg daily, folic acid/iron 1/90mg daily, calcitriol 0.25µg daily, amisulpride 50mg daily, fluoxetine 20mg daily and amitriptyline 25mg per day. No knowledge of drug or food allergies. No personal or family history of angioedema.

Previously healthy until about 1 month ago, the family reported more frequent memory failures and several episodes of disorientation and heteroaggressiveness towards family members, with no other changes. In a private consultation, she has medicated with valproic acid 250mg per day and risperidone 0.25mg per day. Due to the absence of improvement and worsening of the condition, the patient was admitted to the emergency department for symptom control and clarification of the condition.

At the time of admission to the emergency department, the patient presented a condition characterized by an oscillation of the state of consciousness, alternating periods of sustained attention with periods of frank agitation, restlessness, and incoherent speech. After the initial organic evaluation, the patient was diagnosed with acute confusional syndrome, with alterations in the physical, analytical, and imaging examinations compatible with an infectious condition with a respiratory focus (community-acquired pneumonia on the left).

Given the situation presented, and due to the difficulty of administering medication orally due to agitation, haloperidol 2.5mg intramuscular (IM) was administered with rapid control of symptoms. After about 3 hours and due to a new episode of agitation, and due to the good response is shown to haloperidol, 2.5mg IM of this drug was administered again. After about 90 minutes, the patient begins to experience respiratory difficulty with

laryngeal stridor, periocular, lip, and tongue edema, and hypoxia (80% O₂ saturation). Pharmacological treatment with ipratropium bromide, salbutamol (intranasal), hydrocortisone, methylprednisolone, and intravenous clemastine was immediately administered. Intubation with an orotracheal tube was also necessary, and extubation was possible in less than 24 hours. After 6 days, the patient started a new condition during the night period with rapid onset characterized by agitation and restlessness, and haloperidol IM was administered again. Almost immediately, the patient presents with laryngeal stridor, hypoxia, and periocular and lipedema. Pharmacological treatment was immediately administered to reverse the symptoms, again requiring orotracheal intubation. Due to the difficulty in weaning from ventilation and the need for NIV support, she was admitted to the intensive care unit (ICU). During her stay in the ICU, the symptoms worsened, and the patient developed ventilator-associated pneumonia with left pneumothorax, airway obstruction, and consequent worsening of renal failure.

DISCUSSION

In the emergency department, haloperidol is a drug widely used to control agitation when non-pharmacological treatments have failed and when there is a risk of harm to the patient or third parties.

Angioedema has been reported as an adverse effect of several antipsychotics, such as clozapine, risperidone, ziprasidone, and chlorpromazine, however, it is rare as a result of haloperidol administration, with only 4 cases described in the literature⁸⁻¹⁰.

In the case presented, haloperidol was first chosen, not only because it is a very incisive, potent drug with a good profile of side effects, but also because of the possibility of the intramuscular formulation.

Given the good clinical response, this drug was the choice in subsequent episodes. However, after the second administration, a severe hypersensitivity reaction was observed, which can be explained by the excessive production of IgE, which later binds to mast cell

receptors, inducing their degranulation with the release of inflammatory mediators that are responsible for the clinical picture. presented in anaphylactic drug reactions.

This clinical case is important not only to alert to the possibility of side effects, even if considered rare but also to show the importance of clearly defining the procedures to be taken when they occur.

In the emergency department, the high number of patients and the high turnover of professionals make it essential to acquire well-defined measures so that this information is transmitted unequivocally and visibly to all professionals.

CONCLUSION

Haloperidol is an antipsychotic widely used both in hospital and outpatient settings. Due to its effectiveness and side effect profile, it is considered the drug of choice in the emergency department for the control of agitation, being the first line in the symptomatic control of ACS. This drug is also one of the most used drugs in the service of psychiatry and mental health, not only for its antipsychotic potency and effectiveness but also for the possibility of being used in the acute control of symptoms, since it can also be used chronically and in drug formulations. Long term.

Anaphylactic reactions are potentially fatal immune responses that can occur with the administration of any drug. Even when rare or very rare effects are considered, it is important to discuss not only the possibility of severe allergic reactions with the patient when considering starting a new treatment, but also the discussion among professionals of methods of recognition and performance, whether in an outpatient setting or hospital environment.

The realization of sensitization tests, through the supervised administration of the drug in low doses, becomes especially important in long-term formulations, to ensure that hypersensitivity reactions will not occur.

Cases like the one described are rare, and as such, unusual information is valuable that can lead to new research and advances in clinical practice.

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