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Case Report Open Access

Neuroleptic-Induced Oral-Facial Tardive Dyskinesia in a Prepuberal Boy with an Attention-Deficit Hyperactivity Disorder

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Abstract

Background: Patients receiving neuroleptics such as butyrophenone Haloperidol for a long period of time can develop several forms of a rare side effect included among the extrapyramidal dyskinetic syndromes, especially oral-facial involuntary movements called tardive dyskinesia.

Case report: An 11-year-old male patient taking a high dose of haloperidol and methylphenidate in a normal dose for two years was hospitalized due to the severity of the symptoms and eventually the child developed a syndrome of tardive dyskinesia.

Upon admission, medication was stopped and the symptoms disappeared in the next 24 hours. Three days later the boy recovered completely and was discharged from the hospital to follow treatment in the outpatient clinic. There were no recurrences of the dyskinetic reactions during that summer.

Conclusions: Given the possibility of presentation of tardive dyskinesia and other acute extrapyramidal symptoms, we strongly recommend avoiding the prescription of haloperidol, especially associated to methylphenidate (also responsible for some cases of tardive dyskinesia) in the treatment of Attention-Deficit Hyperactivity Disorder (ADHD)

Keywords: Tardive dyskinesia; Attention-deficit hyperactivity disorder; Haloperidol; Side effects; Acute extrapyramidal symptoms

Introduction

The use of antipsychotics, antagonists of dopamine D_2 receptors in the treatment of ADHD in children needs further revision given the incidence of side effects of unknown frequency as tardive dyskinesia and acute extrapyramidal symptoms, both induced by haloperidol [1], and the fact that overdose can produce dangerous morbidity, sometimes even requiring intensive care treatment [2].

We present a case of tardive dyskinesia, the most frequent group of involuntary movements in patient taking haloperidol that causes involuntary facial, oral movements as well as uncontrolled movements of the extremities.

Case Report

During his summer holidays, an 11-year-old boy with Attention-Deficit Hyperactivity Disorder (ADHD), was admitted to A & E department with marked agitation and rapid and involuntary movements of the limbs and fingers (hand flapping). He was complaining of pain in the right side of the mandible, and he developed an acute paralysis of the right facial muscles and palpebral ptosis, that began to recovered around 15 hours after haloperidol withdrawal. The patient was afebrile and the rest of clinical exploration was normal. The boy's weight was 37.5 kg and he was in a normal percentile. No relevant previous diseases were found, except for the ADHD diagnosed when he was 8 years old. The boy had no previous medical history of delirium or movement disorders.

The initial prescription for the ADHD was only methylphenidate that was not successful. Therefore, when the boy was 9 and a half years old, 1.8 mg of haloperidol were added to the dairy 36 mg of methylphenidate and distributed in two doses of 7 drops each, one in the morning and at lunchtime and four drops at night. In our experience, for a boy so small the expected dose should not be more than 1 mg a day of haloperidol.

A blood test was conducted and before the lab tests were returned, the patient developed tongue movements, lip smacking, lip puckering and eye blinking; involuntary movements of the mandible which produced a sharp pain that led to the impossibility of closure of the mouth. Eventually, the patient started to complain of a sensation of swollen tongue with trouble swallowing. This side effect caused a state of heightened anxiety and feelings of agitation and discomfort due to mental over-activity. The patient started to complain of breathing problems.

A new clinical exploration of the patient was performed, with the presence of stiffness of the neck and isochoric pupils that reacted bilaterally with an equal response of both pupils to the light shone in each one of the eyes. No other exploration signs or relevant data for the medical history were found.

In order to exclude signs of inflammation of the meninges, a Computer Tomography Scan imaging was requested. Its results were normal, not reflecting actual clinical-pathologic findings.

The blood test showed concentrations of haloperidol (1.5 µg/L) and very low levels of methylphenidate (<2.0 µg/L). The therapeutic dose oscillates between 8-30 µg/L. The patient had a slight leucocytosis and anaemia, Partial pressure of oxygen (PO_2) and percentage saturation of haemoglobin with oxygen (SO_2) were slightly low [(PO_2=68.4 mmHg and SO_2=94.5%); (normal values: PO_2 between 75.0–100.0 and SO_2 between 95.0%- 98.0%)].

The blood test showed a light hypermagnesaemia (2.5 mg/dL) not related to a large ingestion of magnesium nor with any symptom of renal failure and levels of calcium of 9.70 mg/dL, which are in the upper levels of normal concentration (normal values: 8.89 - 10.0).

With all those symptoms the diagnosis was tardive dyskinesia and the haloperidol was stopped, keeping the same dose of methylphenidate. This withdrawal produced the remission of the neurological disorders in the following 24 hours.

Also, as part of the treatment painkillers were prescribed - dipyrone (metamizol), acetaminophen- dexamethasone (10 mg / 8 hours) and serum eye drops for the treatment of the dry eye syndrome, subsequent to tardive dyskinesia.

Forty-eight hours after hospital admission, the patient was discharged. At that time the levels of magnesium in blood were slightly reduced. The blood test was showing an haloperidol concentration of 0.4 µg/L, a maintained leucocytosis and anaemia. Calcium level was of 9 mg/dL, and blood magnesium levels were of 2.1 mg/dL, being both value considered normal.

Discussion

It has been established that Haloperidol binds to Dopamine D_2 receptors [3] blocking its function in cells and producing an increment of the activity of protein Kinase A (PKA) which has been associated with the activation of the trafficking of alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropioninc acid (AMPA) and N-methyl-D-aspartate (NMDA) glutamate receptors in the same cellular types [4]. Recent articles have shown a relationship between the chronic administration of Haloperidol and an increment of the number of D_3 receptors in the striatonigral neurons and the anterior caudate-putamen area, especially in animals that developed tardive dyskinesia [5]. Also, the dopamine D_1 receptors were reduced in the anterior putamen, the basal ganglia related with involuntary movements [6]. Haloperidol has been involved in the interference in the trafficking of different glutamate receptors in vivo as NMDA associated with calcium-calmodulin dependent kinase in rat frontal cortex [7]. There has also been found a relationship among the block of dopaminergic D_2 receptors and some motor-cognitive impairment in animals with Parkinsonism due to interactions in targeting calcium controlling receptors as NMDA receptors and Vitamin D_3 receptors (VDR) in brain [8]. In fact, the specific activation of the VDR was more effective in protecting motor-cognitive function and neural activity than the inhibition of the NMDA receptor [8]. These results suggest that chronic treatment with haloperidol can induce a tardive dyskinesia due to hyperactivity of glutamate receptors in motor areas in the brain, especially involved in involuntary movements.

If this is a problem in elderly people, it is even a more serious event when it is administrated in children, since adverse effects in humans have been published [2,5,9] and the effect in children has not been established, even though there are evidences in changes in gene expressions of midbrain neurons due to haloperidol administration [6]. For all these reasons we do not recommend haloperidol for the treatment of Attention-Deficit Hyperactivity Disorder in children, at least until new studies have been done.

The fact that tardive dyskinesia in children have been described after an acute intoxication by accidental ingestion [10] wouldn't allow us to discard that the symptoms in our patient were the consequence of an accidental overdose.

Our working hypothesis for the tardive dyskinesia is that a small increment in serum calcium levels produced the hyper stimulation of glutamate receptors. This was firing the appearance of involuntary movements in the facial muscles. Probably, due to the skeletal equilibrium of magnesium and calcium concentrations, to compensate the stimulatory effect of calcium, the plasma magnesium levels were increased. This can be assumed given the fact of the decrement of levels of magnesium only with the withdrawal of haloperidol. We have not found any other article where the levels of magnesium in plasma were determined, which does not allow us to confirm this hypothesis. Then, either a high maintained doses of haloperidol for the child or an accidental overdose by mistake, was producing the syndrome in a patient that has an up regulation of dopaminergic D_3 receptor for chronic treatment with this antipsychotic drug.

Our suggestion is to control the calcium and magnesium levels in patients receiving a chronic haloperidol treatment to prevent these crises.

References

1. Divac N, Prostran M, Jakovcevski I, Cerovac N (2014) Second-generation antipsychotics and extrapyramidal adverse effects. Biomed Res Int 2014: 656370.
2. Collins KO, Comer JB (2003) Maternal haloperidol therapy associated with dyskinesia in a newborn. Am J Health Syst Pharm 60: 2253-2255.
3. Creese I, Burt DR, Snyder SH (1996) Dopamine receptor binding predicts clinical and pharmacological potencies of antischizophrenic drugs. J Neuropsychiatry Clin Neurosci 8: 223-226.
4. Del'guidice T, Beaulieu JM (2008) Messing up with Traffic: different effects of antipsychotic agents on glutamate receptor complexes in vivo. Mol Pharmacol 73:1339-1342.
5. Mahmoudi S, Lévesque D, Blanchet PJ (2014) Upregulation of Dopamine D_3, not D_2, receptors correlates with tardive dyskinesia in a primate model. Mov Disord 29: 1125-1133.
6. Fasulo WH, Hemby SE (2003) Time-dependent changes in gene expression profiles of midbrain dopamine neurons following haloperidol administration. J Neurochem 87: 205-219.
7. Fumagalli F, Frasca A, Racagni G, Riva MA (2008) Dynamic regulation of glutamatergic postsynaptic activity in rat prefontral cortex by repeted administration of antipsycotic drugs. Mol Pharmacol 73: 1484-1490.
8. Ogundele OM, Nanakumo ET, Ishola AO, Obende OM, Enye LA, et al. (2014) NMDA R/+VDR pharmacological phenotype as a novel therapeutic target in relieving motor-cognitive impairments in Parkinsonism. Drug Chem Toxicol 4: 1-13.
9. Sexson WR, Barak Y (1989) Withdrawal emergent syndrome in an infant associated with maternal haloperidol therapy. J Perinatol 9: 170-172.
10. Gajre MP, Jain D, Jadhav A (2012) Accidental Haloperidol poisoning in children. Indian J Pharmacol 44: 803-804.