CASE REPORT

What about temperature? Haloperidol-induced hypothermia

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SUMMARY

The use of treatment with antipsychotic drugs highlights the difficulty of finding the right balance between the benefit on psychotic symptoms and the risk of the occurrence of adverse reactions. There is a strong genetic and pharmacological evidence supporting the hypothesis that activation of D2 receptors could lead to hypothermia and that the treatment haloperidol is capable of inducing hypothermia apomorphino similarly in laboratory animals. It also seems that, haloperidol is not the only antipsychotic able to determine this type of reaction, as some evidence suggests that other drugs such as reserpine, chlorpromazine would be capable of inducing hypothermia. Finally, while some studies suggest the possible occurrence of haloperidol-induced hypothermia only in laboratory animals, other authors argue that this same reaction can occur in humans as well. In this report, we describe the cases, rarely witnessed in the literature, of three patients in whom the administration of haloperidol caused hypothermia.

BACKGROUND

Haloperidol is one of the most used, first generation antipsychotic drugs. It is a selective antagonist of dopamine D2 receptors; it blocks D1 and D2 receptors and also H1 and H2, α 1 and α 2, muscarinic and serotonergic receptors. This drug is widely accessible and may be the only antipsychotic medication available in areas where resources are limited.¹ Extrapyramidal reactions occur frequently with haloperidol, and in most patients these reactions consist of Parkinsonian symptoms (eg, marked drowsiness and lethargy, drooling or hyper salivation, fixed stare).² Apart from the most known collateral effects, no less important than the others, noted in recent times, haloperidol and some other psychotropic drugs such as reserpine and chlorpromazine, induces moderate hypothermia in mice as well as rats.^{3–5} This side effect in humans has rarely been described, and one of the few cases reported, to our knowledge, dates back to 1994. In that year Harada⁶ described a patient with chronic schizophrenia, who had been treated for a long time with chlorpromazine, haloperidol, levodopa, benserazide hydrochloride, diazepam and biperiden, and developed extreme hypothermia (about 32°C) when the dose of haloperidol was increased because of a deterioration in the patient's mental symptoms. No other physical manifestations were observed, except bradycardia. In this patient, the turnover of norepinephrine in the cerebrospinal fluid and blood was increased in association with the hypothermia.

CASES PRESENTATIONS

First case

A female patient, who suffers from 'disorganized schizophrenia', came to Therapeutic Community Rehabilitation in December 2010, from an involuntary psychiatric treatment for the psychomotor agitation in psychotic patient. The patient had no awareness of the illness and the data recorded in the Therapeutic Community Rehabilitation was acquired from the report received by the psychiatric ward and from the interview with her brother-caregiver. The two siblings were in good health and only one of them was married. The patient describes her childhood as quiet, with good family relationships. She graduated with a degree in foreign languages and was an assistant teacher for several years. She was also an esteemed translator and English literature expert. She taught at several high schools until 1995, and previously in Milan from 1983 to 1990. She has been to England four times on study trips and has travelled to Yugoslavia and Switzerland. She is currently single, but had a 4-year relationship with a colleague, which ended in 1995 (the year her contract expired and her first hospital admission). It appears that the patient has suffered from mental illness for about 20 years, characterised by a persecution complex which led to a progressive decline in her skills, the patient was admitted on numerous occasions for these symptoms. Since her mother's death from heart disease in October 1998, she interrupted each treatment, but still living with a severe mental illness. During the mental assessment made at the time of admission, the patient seemed to have neglected herself, used exaggerated gestures and appeared hostile. Her mood was dysphoric, her thoughts were disorganised, focused on feelings of persecution and grandeur. It came to our attention that during her stay at the hospital, she took 10 mg $\times$ 3 haloperidol for a couple of months, which was further increased, owing to the persistence in the psychotic symptoms. Owing to her refusal of psychiatric patient status and her lack of compliance, it was necessary to change the treatment, changing the oral therapy to 150 mg haloperidol fl. intramuscularly 1/28 days. After receiving three doses, the patient appeared to behave in a more orderly fashion and was much more restrained in her delusions of grandeur (even if it was still present). Although the thymic axis appeared to be fairly balanced, the only really negative aspect was the total lack of awareness about her illness and she was consequently reluctant to accept treatment. The latter was displayed by the

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manifestation of a variety of psychosomatic symptoms (fatigue, mood swings and other symptoms), which the patient linked to the administration of the vial.

After about 4 months, owing to the continuation of this subjective unspecified distress, arrangements were made for periodic monitoring to be carried out of the vital signs such as blood pressure, blood heat and glycemia. The patient's daily measurement of CT values in the course of a month ranged from 34.6°C to 33.2°C, with an average of 34°C. This state of mild hypothermia presented circadian fluctuation with a drop in blood temperature in the morning, conforming with the patient's general feeling of malaise.

Second case

A 24-year-old male patient is the first-born of three children. The parents told us that his maternal grandfather was cantankerous and often violent. He squandered the family inheritance in the space of a few years as a result of disastrous business investments and lecherous behaviour. The patient's mother also explained that he had had a difficult neonatal period, due to the appearance of a duodenal atresia which was surgically corrected.

The patient remembers his childhood as peaceful. He states that he had always been sociable and exuberant. After leaving middle-school, he decided to go to one of the state high schools in his town, but at the end of the third year, he was kept down because of numerous absences. Therefore, he decided to enter a private school, but 2 months later he was expelled, owing to a severe argument with a teacher who caught him taking drugs. The patient also states that he is still a regular cannabis user, which he uses mainly to calm down his continual state of tension. Later on, he was accepted at another private institute but he left after a few months as he decided to quit school once and for all and to start a job as a web-master, using his supposed technical skills. In order to carry this out more easily, he moved to Milan, staying with some friends of his parents. His mother says that substantial amounts of money were sent to him regularly, so as to fund undisclosed expenses. He was involved in a sequence of serious road accidents dating back to 2011: however, despite the severity of the injuries, he remained uninjured. Owing to these circumstances, the patient returned to the family house. His mother remembers that he stayed at home for about a month, refusing to see anybody and refusing to eat. At that time, he underwent a weight loss of approximately 10 kg, but after this period, the mother claims that he had regained a certain equilibrium.

The patient came to our attention because after his maternal grandfather's death in 2012, his mother claimed to have observed him behaving very tensely once again and heard him having 'strange conversations' about a job carried out on behalf of a major pharmaceutical company and a supposed fiancée, who he claimed to be a rich Russian heiress. At that time, he also accumulated large debts with some friends by buying electronic accessories and renting a high-powered car for his alleged working activities.

The patient arrived looking stylish and sophisticated for his examination. Initially, he appeared suspicious and mistrustful of the medical personnel and his mood seemed dysphoric at times. From the interview, there was thought disorders and a focus on feelings of grandeur and sexual matters. The patient claimed that he was spending all night working at the computer and said that he did not need a doctor for of his abundance of energy. The patient showed no perception of his situation.

In this case, the treatment recommended was valproate 900 mg/daily and haloperidol 2 mg/daily. However, owing to his

lack of compliance and the irregular taking of the prescribed medication, the administration of haloperidol 150 mg intramuscularly every 4 weeks was prescribed. After the first four doses, thought disorders appeared to be more moderate and his sleep more regular. Nevertheless, he experienced weight loss, and the patient reported having chills and fatigue especially in conjunction with the administration of the vial. In some circumstances, his mother had found a body temperature to be 34–35°C. For this reason it was recommended that his body temperature be recorded for the 28-day period and it showed that this fluctuated from 34.2°C to 35°C with an average of 34.6°C.

Third case

The patient came to our attention in March 2012. The woman is the only child and she remembers her childhood as being peaceful, and that she did well at school and got on well with her peers. The patient also said that she was deeply affected by her father's death as she was very close to him. The patient recounts that she met her husband when she was 21 years and married him at the age of 26. One year later, she became a mother. At the age of 34, the marriage broke down and they were divorced due to their incompatibility. She had a variety of jobs, a bar cashier, a secretary in a legal department and as a call centre operator. The patient reported that she had been hospitalised in 2002 for unspecified mental disorders, then in September 2011, she returned to the same hospital unit with symptoms characterised by thought process disorders, she was then discharged with the diagnosis of 'delusional disorders' (DSM IV-TR). During the mental assessment made at the time of her admission, the patient appeared clean and neat, but wore a hostile expression. She appeared suspicious of the health worker in that she made repeated requests not to take any notes about the medical examination. Her mood was dysphoric, with her thoughts focused on a persecution complex, making reference to the 'evil eye' and a neighbour's envy of which the patient believes to be a victim. After this visit, the patient began once again to take the treatment prescribed on the previous admission: haloperidol 50 mg intramuscularly every 4 weeks for several months. After approximately 6 months, she returned to her doctor because of gradual weight loss and a general feeling of malaise. After undergoing blood tests, which were recommended by her doctor, the results came back as normal, therefore we decided to record her vital signs periodically, such as blood pressure, blood temperature and glycaemia. From the values taken over a month, the patient's body temperature daily measurement ranged from 34.8°C to 33.6°C, with an average of 34°C.

TREATMENT

In the first case, it was decided to switch the haloperidol therapy to risperidone fl. intramuscularly 50 mg every 2 weeks. In the second case, it was decided to switch the haloperidol therapy to risperidone fl. intramuscularly. 50 mg every 2 weeks. In the third case, it was decided to stop the haloperidol therapy and to introduce oral administration of olanzapine 10 mg/day.

OUTCOME AND FOLLOW-UP

Patients continued treatment with olanzapine and risperidone and, currently, at follow-up visits, vital parameters are regularly monitored to show the possible occurrence of adverse reactions.

DISCUSSION

Hypothermia is defined as a decrease in core body temperature (CBT) under 35°C. The condition is classified as mild when

CBT is from 35°C to 32°C, moderate when it is from 32°C to 30°C, and acute when it is below 30°C.⁷ In the cases above mentioned, allowing the correlation between the drug and CT taken, it would be mild hypothermia cases. The aetiology of hypothermia can be primary or secondary. The first occurs as a result of a spontaneous persistent decrease in the internal temperature (diving in cold water, unsuitable protective clothing in cold environments, etc). The second occurs in a normal temperature environment as a result of a decrease in the production of heat (endocrine disorders, insufficient energy supply, neuromuscular disease, etc), or because of a major heat loss (induced vasodilatation, skin diseases, iatrogenic causes, etc) or due to thermoregulation disease (trauma, brain tumour, multiple sclerosis, anorexia nervosa, etc).⁸

The cases aforementioned, currently treated with haloperidol, are all examples of secondary hypothermia due to thermoregulation disease.

Haloperidol, a butyrophenone derivative, is an antipsychotic drug that acts as a selective antagonist of the dopamine D2 receptors.⁹ The D2 receptors are expressed, at relatively high levels, in the cortical regions, especially in the limbic area. These high levels of D2 and D3 receptors suggest that these receptors are one of the major drug targets for the treatment of a various psychiatric and neurological disorders, including Parkinson's disease, restless legs syndrome, depression and schizophrenia.^{10–12} It is also documented that haloperidol, as some other psychotropic drugs, such as reserpine and chlorpromazine, induce hypothermia in mice and rats. The results of several studies on neuroleptic thermoregulation suggest that neuroleptic systemic injection generally causes hypothermia in humans and animals that are in normal temperatures room.^{13 14}

Learning points

- ▶ Hypothermia in patients treated with haloperidol is an adverse reaction rarely reported in the literature.
- ▶ It is good to monitor vital parameters in patients taking antipsychotic for the first time.
- ▶ The switch of therapy from haloperidol to olanzapine or risperidone showed an improvement of the condition of hypothermia.

Chronic hypothermia can result in haematological effects, in particular the increase in blood viscosity, fibrinogen and haematocrit; these disorders can affect the function of many organs. Hypothermia has also been reported as a cause of suppression and medullar insufficiency, as well as of anaemia, which is the reason why it is important to detect this side effect.

Contributors FN and MB identified and managed the cases. SF has the idea and wrote the manuscript. EA revised it critically for important intellectual content.

Competing interests None.

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