De Novo delayed onset hypothermia secondary to therapeutic doses of risperidone in bipolar affective disorder

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Ther Adv Psychopharmacol

2014, Vol. 4(2) 70–74

DOI: 10.1177/

2045125313507740

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Abstract: The commonly reported side effects related to risperidone include dizziness, nausea, weight gain, sleep disturbances, and sexual dysfunction. A rather rare and very much less documented side effect of risperidone is hypothermia: traditionally defined as a drop in core body temperature below 35°C (95°F). We report a case of a 75-year-old woman who had been treated for bipolar affective disorder for nearly 3 years with risperidone went on to develop hypothermia which was reversed with the withdrawal of the offending drug. This case is unique as it reported a rare but potentially serious side effect occurring after a prolonged administration of risperidone contrary to the previous reports in which hypothermia occurred only a few hours or days after the administration of risperidone and occurred in a patient who was diagnosed as having bipolar affective disorder as opposed to schizophrenia, the most common psychiatric disorder associated with previously reported hypothermia. The authors would like to emphasize the importance of this idiosyncratic potentially life-threatening adverse effect of risperidone-induced hypothermia to all clinicians, which occurs regardless of the duration of drug intake, in order to help them identify the condition early and treat it effectively.

Keywords: bipolar affective disorder, delayed onset, hypothermia, risperidone

Introduction

The invention of chlorpromazine, a first-generation antipsychotic, in 1950 by Pierre Deniker and Jean Delay heralded a major revolution in the field of psychopharmacology. While the worrisome extrapyramidal side effects that are frequent with most of the first-generation antipsychotics were offset at least partially by the advent of second-generation antipsychotics, unfortunately these second-generation drugs have potentially serious side effects of their own.

Risperidone, a benzoxazole derivative is a widely used second-generation antipsychotic drug which exerts its action via the blockade of dopamine (D2) and serotonin (5HT2) receptors in the limbic system. The commonly reported side effects related to risperidone include dizziness, nausea, weight gain, sleep disturbances, and sexual dysfunction, which is secondary to hyperprolactinaemia. A rather rare and very much less documented

[Razaq and Samma, 2004] side effect of risperidone is hypothermia: traditionally defined as a drop in core body temperature below 35°C (95°F) [Lalith *et al.* 2011]. Hypothermia in patients using an antipsychotic drug is a serious, unpredictable, type B adverse event frequently leading to hospital and intensive care unit (ICU) admission and sometimes even to death [van Marum *et al.* 2007]. While the hypothermic effects of antipsychotic drugs are less well known as opposed to the hyperthermic effects such as malignant neuroleptic syndrome [Hägg *et al.* 2001], none or a few if any cases were reported with the use of risperidone in warm tropical countries in areas such as Asia.

Here we report a case who has been treated for bipolar affective disorder for a considerable period of time with risperidone in a South Asian country, who went on to develop hypothermia which was reversed with the withdrawal of the offending

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drug. The authors would like to emphasize, by reporting this case, the importance of knowledge of the occurrence of this idiosyncratic adverse effect regardless of the duration of drug intake to all clinicians in order to help them to identify risperidone-induced hypothermia early and to treat the condition effectively.

Case report

A 75-year-old woman was admitted to a tertiary psychiatric facility in Sri Lanka in February 2012 with a 1-week history of increased speech and activity and poor sleep suggestive of a manic episode. She had been diagnosed as having bipolar affective disorder from her late teens and had been treated with several antipsychotics, both typical and atypical, in addition to mood stabilizers during past relapses and as maintenance. She was noncompliant with treatment 6 months prior to the current admission. The corroborative history from her family members revealed that her treatment adherence was generally poor resulting in relapses approximately once in every 3 years. Most of these were manic episodes and according to the medical records she had been hospitalized for inpatient treatment nearly ten times in the past. However, in between the episodes she had been functioning relatively well. According to her personal history her husband passed away 10 years ago and she had five grown-up children who provided her with good care and support. She had a strong family history of mental illness as one of her sisters was diagnosed as having bipolar affective disorder and was on medication. She did not have any significant medical history or history of psychoactive substance use in the past.

Her mental state examination on admission revealed her mood was elated and she did not have any psychotic features. She was well oriented but had poor insight regarding her mental state. Her vital functions were normal. She had to be sedated with 5 mg of intramuscular haloperidol on admission as she was disturbed and she failed to calm down with oral sedative drugs. Her medication history revealed that she had been well stabilized with risperidone 4 mg twice daily and sodium valproate 400 mg twice daily for about 3 years prior to her reducing the medications on her own by halving the doses of both medications (risperidone 4 mg once daily and sodium valproate 200 mg twice daily) during the last 6 months. She was recommenced with the previous

dose of psychotropic medications of risperidone 4 mg twice daily and sodium valproate 400 mg twice daily on admission and she needed occasional sedation with oral lorazepam 1 mg for her agitated behavior and poor sleep.

With time (a day after the admission) she developed slurred speech due to extrapyramidal side effects and subsequently benzhexol 4 mg daily was added and risperidone dose was reduced to 4 mg at night. Her extrapyramidal symptoms resolved with the above dose adjustment of the psychotropic medications on the third day after admission. As she developed drowsiness (4 days after admission), lorazepam was omitted. An urgent computed tomography (CT) scan of the brain was performed which was normal and the drowsiness settled with the omission of lorazepam the following day (5 days after the admission). However, a week after admission, she became markedly drowsy again without any sedatives such as benzodiazepines. She was found to be mildly dehydrated though she was hemodynamically stable and the rest of the physical examination was normal. She was afebrile and her capillary blood sugar level was normal. She was urgently transferred to the medical unit for further assessment and medical care. Her full blood count, renal function tests, liver function tests and creatine phosphokinase levels were within normal limits and erythrocyte sedimentation rate was marginally elevated. However, her electrocardiogram showed a 'J' wave (Figure 1) suggestive of hypothermia and a heart rate of 65 beats per minute, which was normal. Her body temperature was measured as 92°F (33.3°C) which indicated she was suffering from hypothermia. Her body temperature was closely monitored and she was warmed with blankets and application of external heat with hot-water bottles. The treating consultant physician suspected that the hypothermia was induced by antipsychotics and hence withheld risperidone while continuing sodium valproate and continued supportive care and close monitoring. In addition she was prescribed intravenous antibiotics since she had clinical and radiological evidence of lower respiratory tract infection such as productive cough and bilateral multiple opacities in the chest X-ray. Her hypothermia settled within a week as the temperature picked up to 98.5°F, thus the treating physician ascertained that the patient suffered from risperidone-induced hypothermia. The repeat ECG revealed the disappearance of J waves (Figure 2).

Figure 1. Electrocardiogram (ECG) obtained at the time of hypothermia showing J waves.

Figure 2. The repeat electrocardiogram (ECG) taken after the return of normothermia showing the disappearance of J waves.

Since her manic symptoms persisted, haloperidol 3 mg twice daily was added to her medication regime and her manic symptoms subsided with time. She was psycho-educated about the illness and the use and side effects of the medications, especially regarding hypothermia and the measures to be taken at home with regards to this. Nearly a month after admission, she was discharged from the ward and has been followed up in the outpatient clinic to date. She had been compliant to the medication regime and was functioning well. She tolerated the medications fairly well and had not had any hypothermic episodes so far.

Discussion

This case is unique as it reports a rare but potentially serious side effect occurring after a

prolonged administration (nearly 3 and 1/2 years) of the offending drug contrary to the previous reports in which hypothermia occurred only a few hours or days after the administration of the index medication. Moreover, the patient in this case report was diagnosed as having bipolar affective disorder as opposed to schizophrenia, which was the most common psychiatric disorder associated with previously reported hypothermia [van Marum *et al.* 2007]. Finally the occurrence of this side effect in a patient living in a country with a warm climate also highlights the importance of this case as in comparison with previous reports [Kreuzer *et al.* 2012; Schwaninger *et al.* 1998].

The onset of hypothermia is considered 'delayed' as the patient developed hypothermia following continuous treatment of risperidone for nearly

3 and 1/2 years. The patient had been taking risperidone 4 mg twice daily for 3 years before she herself reduced the dose to 4 mg once daily. The dose of risperidone was increased to 4 mg twice daily on the day of admission to the hospital, but reduced to 4 mg at night a day after the admission and hypothermia developed a week after the admission.

Antipsychotic drugs can influence thermoregulation and even before its psychotropic properties were made clear in the early 1950s, the first manufactured antipsychotic medication, chlorpromazine, was used to suppress compensatory responses to body cooling in surgery (artificial hibernation) [Hägg *et al.* 2001]. In clinical practice, the most common causes of hypothermia are prolonged exposure to cold temperature as well as extremities of age, malnutrition, hypoglycemia, adrenal insufficiency, hypothyroidism, diabetes mellitus, stroke, disability, sepsis, shock, burns and exfoliative dermatitis [Hägg *et al.* 2001]. The presence of lower respiratory tract infection in this patient might have contributed to the hypothermia in addition to the drug effect, but the reversal to normal temperature upon the withdrawal of risperidone clearly indicates its causation. Conversely, the patient received intravenous antibiotics which would have helped in the resolution of the respiratory infection leading to improvement in temperature, which may have coincided with the cessation of risperidone and thus challenging its causation. Hypothermia results in progressive depression of all organ systems. Depending on the severity of the hypothermia, patients may show various clinical manifestations from shivering and a feeling of coldness to deep coma [van Marum *et al.* 2007] and this patient had marked drowsiness due to hypothermia which was reversed with the reappearance of normal body temperature. Notably a substantial proportion of unexplained deaths should be attributed to antipsychotic-induced hypothermia [Kreuzer *et al.* 2012]. Apart from risperidone, hypothermia has been reported after the use of atypical antipsychotic medications such as ziprasidone [Gibbons *et al.* 2008] olanzapine, aripiprazole, quetiapine, clozapine, sulpiride, amisulpiride and most of the typical antipsychotics [Hägg *et al.* 2001] including chlorpromazine, trifluoperazine and haloperidol and even with the mood stabilizers such as sodium valproate [Tubb *et al.* 2009].

Although the exact mechanisms are unknown, hypothermia which is associated with antipsychotic

medication use seems to have several possible causes. Van Marum and colleagues described four hypotheses [van Marum *et al.* 2007]. First, the role of a drug-receptor profile, as serotonin is associated with thermoregulation and the atypical antipsychotics such as risperidone have stronger affinity for the 5-HT_{2a} receptor than for the D₂ receptor and thus are associated with hypothermia. In addition, some antipsychotics such as chlorpromazine, risperidone and clozapine block Alpha₂-adrenergic receptors which are also involved in thermoregulation, by inducing peripheral responses to cooling (vasoconstriction and shivering) and lead to hypothermia. Second, damage to certain areas of the brain such as the pre-optic anterior hypothalamic region, which regulates body temperature, which may be noticed in some patients makes them more susceptible to hypothermic effects of antipsychotics. Third, antipsychotics induce apathy and indifference by dopamine blockage which impairs awareness and subsequent behavior aimed at protection against the cold, such as putting on extra clothes and therefore leading to hypothermia. Finally, the co-existence of infections at the time of development of hypothermia might play a role in the deregulation of thermal homeostasis as in this patient. In addition to these mechanisms, neurotensin (NT), which is one of the most important thermoregulatory peptides, has been recognized as a mediator of hypothermia in patients with schizophrenia, as NT concentration in the cerebrospinal fluid (CSF) is low and is usually normalized following antipsychotic drug use in patients with schizophrenia [Sharma *et al.* 1997]. NT may also be involved in antipsychotic-induced hypothermia.

With regards to the management of the patients with hypothermia, the aggressiveness of treatment is matched to the degree of hypothermia. Treatment modalities include noninvasive, passive external warming (the use of a person's own heat-generating ability through the provision of properly insulated dry clothing and moving to a warm environment), active external rewarming (applying warming devices externally such as warmed forced air), to active core rewarming (the use of intravenous warmed fluids, irrigation of body cavities with warmed fluids, such as the thorax, peritoneal, stomach or bladder), the use of warm humidified inhaled air and the use of extracorporeal rewarming such as via a heart lung machine [McCullough and Arora, 2004]. Blankets and hot water bottles were used to warm this patient, which proved to be very effective.

The primary purpose of this report is to emphasize a rare but a recognized and potentially life-threatening adverse effect of risperidone-induced hypothermia. As risperidone is widely used in psychiatric settings in many parts of the world, all physicians should therefore be familiar with this unwanted effect as early recognition and rewarming at the earliest possible time brings about certain complete recovery. In addition, the authors would like to caution physicians that this case report also raises the possibility of hypothermia developing in patients receiving risperidone irrespective of the duration that they take the medication and to emphasize the importance of educating the treating physicians as well as the patients and their family with regards to the identification and remedy of this sinister adverse effect of risperidone.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of interest statement

The author declares that there is no conflict of interest.

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