

Heat stroke in schizophrenia during clozapine treatment: rapid recognition and management

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Abstract

A case of heatstroke is reported in a 32-year-old man diagnosed with schizophrenia and on clozapine monotherapy. The importance of the need to avoid misdiagnosing heat stroke as neuroleptic malignant syndrome is reviewed.

Keywords

clozapine, heat stroke, neuroleptic malignant syndrome, neuroleptics, schizophrenia

Introduction

Heat intolerance in schizophrenia treated with dopamine blocking neuroleptics is a rare but well recognized phenomenon in hot climates (Bark, 1998). The pathophysiology of this phenomenon relates to the role of dopamine within the hypothalamic thermoregulatory pathways, which are located within the preoptic hypothalamic area (Cox and Lee, 1977). Interruption in dopaminergic transmission in the hypothalamus prevents animals from coping with a heat load (Cox *et al.*, 1978), and it may be assumed that intrinsic dopaminergic abnormalities associated with the disease itself (Sunahara *et al.*, 1993) may further impair thermoregulation. Those working in the field of psychiatry will be familiar with the T-shirt in winter and duffle coat in summer syndrome in severely mentally ill patients, which belies a thermoregulatory deficit.

Heat stroke is a medical emergency, with the two cardinal features being raised core body temperature (> 40 °C) and central nervous system dysfunction; it may be fatal in up to 50% of cases (Bouchama and Knochel, 2002); multi-organ injury ensues when the core temperature rises substantially. We wish to report a relevant case in a patient with schizophrenia, which occurred in the UK during a heat wave in August 2002. The patient was referred to R.K. as a potential case of neuroleptic malignant syndrome (NMS). One essential aim of reporting this case is to highlight the need to avoid misdiagnosing heat stroke as NMS, which could have fatal consequences.

Case report

The patient was a 32-year-old male with a diagnosis of paranoid schizophrenia and a significant forensic history. Subject to section 37/41 of the Mental Health Act, 1983, he was living in the community under conditional discharge arrangements. He had a history of neuroleptic non-responsiveness but had recovered substantially for the benefit of clozapine 200 mg twice daily and was in gainful employment as a builder's labourer. He also had a history of alcohol, glue, cocaine and cannabis abuse, but his status in this respect at the time was unquantified.

On the day of admission, in August 2002, he was found unconscious and fitting on an open building site. On arrival at his local Accident and Emergency Department, he suffered a respiratory arrest, had a raised temperature of 42.9 °C, was hypotensive (90/60 mmHg) and had the minimum Glasgow coma scale score of 3; there were no signs of extrapyramidal rigidity. He received active cooling, was ventilated, given dantrolene and was admitted to the intensive care unit.

Initial investigations revealed an elevated creatinine phosphokinase (CPK) level of activity of 6000 U/l (24–195 U/l) and a normal white blood cell count (WBC) of $10.3 \times 10^9/l$ (4.3–10.8 $\times 10^9/l$). By the second day, CPK level of activity had risen to 30 000 U/l with fulminant liver failure as judged by an alanine aminotransferase activity of > 7000 U/l (5–30 U/l) and an international normalized ratio of > 8, he was transferred to a liver intensive care unit.

The patient was then referred to R.K. as a potential case of NMS. The clinical picture was dominated by ongoing liver failure, acute tubular necrosis due to rhabdomyolysis, adult respiratory distress syndrome (ARDS), neutropenia and disseminated intravascular coagulation. He required intensive support for 4 weeks involving ventilation anaesthesia, antibiotics, haemodialysis and granulocyte colony stimulating factor.

He was subsequently transferred to his local intensive care unit and thence onto a stroke rehabilitation unit where he made an uneventful physical recovery. He is currently showing no signs of a psychotic illness and is antipsychotic-free. He requires intensive physiotherapy as a result of muscle necrosis and is described as mentally slow; however, no details of cognitive functioning have been recorded.

An aftercast of the weather conditions obtained from the national meteorological office showed a temperature of 26 °C at the time of discovery, this was also in the middle of a 3-day heat wave, and it is not known how long he had lain undiscovered.

Discussion

This patient was originally considered to be suffering from NMS but the clinical picture was very much against this and strongly in favour of heat stroke. Most particularly, he did not have extrapyramidal rigidity and the hyperthermia was uncharacteristically severe for NMS. Furthermore, the WBC was initially normal and neutropaenia subsequently developed; this is in contrast to the raised WBC typically found in NMS. Liver failure, early rhabdomyolysis and ARDS are the most serious complications of heat stroke and ensue when the condition is not treated early (Yaqub and Al Deeb, 1997); however, some of these complications may also occur in NMS. Although the CPK was very high, it should be noted that this is a confirmatory aspect to NMS, where the characteristic syndrome prevails. In addition, heat stroke is also associated with very high CPK levels.

In comparison with other neuroleptics, clozapine is not a potent dopamine (D₂) receptor blocking drug, although, there is substantial literature to demonstrate its dopamine blocking activity within limbic structures (Pilowsky *et al.*, 1997). However, it should be noted that hypothalamic dopamine receptor occupancy is not directly measurable using functional imaging techniques. In addition, clozapine is a potent antimuscarinic agent, and this is another factor that may influence thermoregulation (Lin *et al.*, 1980).

In conclusion, neuroleptic drugs are a risk factor for fatal heat stroke (Fijnheer *et al.*, 1995); psychiatrists in temperate climates may not recognize this, and may misdiagnose the condition as NMS, which could have fatal consequences. However, no reports of heatstroke in relation with clozapine were identified in a literature search. Early differential diagnosis between heat stroke and NMS allows prompt instigation of the appropriate, and potentially life-saving treatment. Although 26 °C (79°F) is not exactly a 'scorcher', it must be remembered that neuroleptic drugs paralyse thermoregulation (Cox *et al.*, 1978) and clinicians should be on the look out for this syndrome in summer.

In terms of the future clinical management of this patient, clozapine could certainly be restarted; however, his treating clinician decided on an initial period of neuroleptic-free assessment. When clozapine or other neuroleptics are reintroduced, thorough education regarding safety during hot weather should be provided, both to the patient and his carers; this should be reinforced at regular intervals during continued treatment.

Implications for clinical care

Prevention Heat stroke results from exposure to high environmental temperature (classical heat stroke) or from strenuous exercise (exertional heat stroke). It is recognized that those who are socially isolated or with chronic mental disorders are amongst a group who are particularly at risk of developing heat stroke; moreover, this group may well be taking medications that increase the risk of developing heat stroke (e.g. anticholinergic drugs which impair sweating or neuroleptic drugs which interfere with thermoregulation). Psychiatric patients may also fall into other categories of those who are particularly at risk of heat stroke. This includes the very young and elderly, alcoholics, those with cardiopulmonary disease and those taking other medications (e.g. diuretics which interfere with salt and water balance).

However, heat stroke is not totally preventable, although knowledge of the disorder could reduce morbidity and mortality. Prevention may be achieved by people acclimatizing themselves to heat, avoiding being outside at the hottest times of the day, reducing levels of physical activity, drinking additional water and consuming salty foods, and by spending plenty of time in air-conditioned environments, if available.

Doctors prescribing neuroleptic drugs should inform their patients of the particular risks of hot environments, with the difficulty in the UK being that people are generally less aware of the dangers of hot weather because hot weather occurs for such a short period in any given year. However, with the possibility of a changing climate due to global warming, the need for education about heat stroke for psychiatric patients in the UK may well become more pressing. This education could include issuing reminder cards when neuroleptics are dispensed, or increasing awareness by displaying information leaflets and posters in outpatient clinics and community mental health centres. Holidays abroad are also more commonplace, and patients should be also reminded about keeping safe in hot climates if they intend to visit hot countries.

Recognition Early signs of heat stroke may be subtle manifestations of brain dysfunction (e.g. inappropriate behaviour, restlessness, impaired judgement or confusion) in hot environmental conditions or after exertion. However, heat stroke usually starts with sudden collapse, with central nervous system (CNS) symptoms ranging from drowsiness to coma, and collapse is not usually preceded by heat cramps or heat exhaustion.

For clinicians trying to make a diagnosis in a critically ill patient, the clinical signs of established heat stroke include a core body temperature > 40 °C, accompanied by hot, dry skin and central nervous system abnormalities such as delirium, convulsions or

coma. Seizures may occur, particularly during cooling. There is always tachycardia and hyperventilation, 25% have hypotension. Laboratory investigations on admission may reveal respiratory alkalosis, hypophosphataemia, hypokalaemia, raised creatinine kinase, leukocytosis and an altered level of lymphocytes.

The most serious complications of heat stroke are those of multi-organ dysfunction, including encephalopathy, rhabdomyolysis, acute renal failure, adult respiratory distress syndrome, myocardial injury, hepatocellular injury, intestinal ischemia or infarction, pancreatic injury and haemorrhagic complications, particularly disseminated intravascular coagulation with pronounced thrombocytopenia.

Prompt diagnosis and treatment of heat stroke prevents fatal multi-organ insult, and a thorough search for other causes of hyperthermia associated with coma or CNS disturbance should be made at the time of presentation. The differential diagnosis includes sepsis, neuroleptic malignant syndrome and malignant hyperthermia.

Management Early recognition and prompt treatment reduces the high mortality associated with heat stroke. The patient should be admitted to hospital, where the two main objectives for emergency management are rapid evaporative cooling and support of vital organs. Cooling is achieved by applying cold water or ice to the skin, which is fanned. In addition, cutaneous vasoconstriction should be prevented by vigorous massage or spraying with tepid water. As yet, there are no pharmacological agents helpful in accelerating cooling in heat stroke; dantrolene has been used, but there

is no clear evidence of its effectiveness. Support of vital organs may require admission to an intensive care unit.

Neuroleptic drugs may be reinstated once the patient is medically stable, but should be accompanied in due course by education, both to the patient and their carers, about prevention of heat stroke and safety during hot weather.

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