FATAL EXERTIONAL HEAT STROKE IN A PATIENT RECEIVING ZUCLOPENTHIXOL, QUETIAPINE AND BENZTROPINE

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ABSTRACT

Objective
To report a case of fatal exertional heat stroke associated with the use of zuclopenthixol, quetiapine and benztropine.

Case Summary
A 36-year-old male with a history of schizophrenia and bipolar disease was working as a roofer during the third day of a heat wave. His medications included zuclopenthixol, quetiapine, benztropine, carbamazepine and levothyroxine. He developed loss of consciousness late in the day and presented to hospital with a Glasgow Coma Scale 3 and a rectal temperature of 42.2^{0}C. He progressed to severe multiple organ dysfunction and asystole, and expired the following morning. Neuroleptic and anticholinergic agents have long been associated with heat alteration, but there are few reports involving the newer antipsychotic agents. Physicians and pharmacists should ensure that appropriate counseling is given to patients receiving these medications regarding early recognition of signs and symptoms and prompt treatment of heat related illness and heat stroke.

Key Words: *Heat, heat stroke, fatal, zuclopenthixol, quetiapine, benztropine, antipsychotic*

Human beings are homeotherms and utilize a combination of behavioral and physiological mechanisms to maintain their core body temperature within a relatively narrow range of 36.2°C to 38.2°C. Heat related illnesses are syndromes of physiological injuries that result from an environmentally induced elevated body temperature.[1] A large number of fatal cases seen today have involved military personnel undergoing training for deployment in hot, humid weather or in tropical regions, or athletes training for various events. Heat stroke is a leading cause of death, second only to head and spinal cord injuries, among American athletes.[2] In addition to a hot environment, other factors have been implicated in the pathogenesis of classical heat stroke, including the concomitant use of prescription medications, or exposure to exogenous chemicals such as those used in agriculture and industry. A number of medications can interfere with the body's ability to regulate normal body temperature during exercise or under conditions of environmental heat stress.[3,4] We present the first reported case of fatal exertional heat stroke associated with the use of zuclopenthixol, quetiapine and benztropine.

CASE REPORT

On May 29, 2006, the 3rd day of a heat wave in Southwestern Ontario, the temperature rose to 33.1°C with a humidex of 40°C. A 36-year-old male roofer, with a history of a schizo-affective disorder, was working with appropriate work clothing and safety hat. His colleagues indicated that he was drinking water intermittently. By the late afternoon he complained of headaches and was speaking incoherently. He was instructed by the foreman to come down from the roof and get into the truck. As he was trying to change his clothes, he fell and hit his head on the truck and lost consciousness. An ambulance was called and

he was transferred to the local hospital. His medications at the time included zuclopenthixol 20mg at bedtime, quetiapine 1000mg at bedtime, benztropine 2mg at bedtime, carbamazepine 400mg twice daily, and levothyroxine 0.05mg daily. We confirmed with his regular dispensing pharmacy that he was compliant with his medications.

The patient arrived at the local hospital 35 minutes later and was found to be unresponsive with a Glasgow Coma Scale of 3 and a rectal temperature of 42.2°C. The patient was intubated immediately for airway protection and oxygenation. The patient received aggressive fluid resuscitation and cooling with ice packs to head, axillae and feet. Initial blood work and examination revealed renal and hepatic impairment, a combined metabolic and respiratory acidosis, and elevated total CK. He went on to develop wide complex tachycardia and dark sanguineous nasogastric drainage. The patient's temperature had come down to 39.1°C 3 hours after arriving to the local hospital and the treating physician called our tertiary centre to accept this patient in transfer.

The patient arrived in the Intensive Care Unit 5 hours after the initial event. He continued in respiratory and renal failure, hemodynamic shock and further developed disseminated intravascular coagulation (see Table 1). Despite aggressive fluid resuscitation, vasopressor therapy, antibiotics, transfusions of fresh frozen plasma and cryoprecipitate, the patient developed asystole the following morning and could not be resuscitated.

TABLE 1 Laboratory Parameters

Time	May 29 2240h	May 30 0135h	May 30 0530h
Arterial pH	7.22	7.22	7.14
Arterial pCO_2 (mmHg)	30	30	40
Arterial HCO_3 (mmol/L)	12	12	13
Arterial Lactate (mmol/L)	2.9	3.9	8.6
Serum Urea (mmol/L)	9.1	11.2	13.6
Serum Creatinine (umol/L)	276	320	357
WBC $x10^9$ /L	24.4	22.4	23.7
INR	1.6	3.6	2.2
PTT (s)	62	>150	58
Serum ALT (U/L)	208		718
Serum AST (U/L)	550		1110
Serum Troponin-I (ug/L)	5.21		9.83
Serum Myoglobin (ug/L)	>4000		
CK (U/L)	29 724		30 384
Amylase (U/L)	256		

DISCUSSION

Environmental hyperthermia syndromes are a reflection of human maladaptation to high ambient temperature and humidity. Heat stroke is the most severe form of illness characterized by a core temperature greater than 40°C, central nervous system abnormalities such as delirium, seizures, coma and multiple organ dysfunction resulting from exposure to environmental heat stress. There are two types of heat stroke. In classical heat stroke, extremes of temperature exceed limited physiological reserves and the ability to lose heat. Exertional heatstroke is a result of endogenous heat production far exceeding the body's ability to shed heat.[5-10]

In addition to a hot environment, other factors have been implicated in the pathogenesis of heat stroke. The use of prescription medications or exposure to chemicals can cause drug related fevers through various mechanisms.[11-15] Medications implicated in the pathogenesis of heat stroke are divided into two broad groups of those that impair heat loss and those that increase heat production. Neuroleptic and anticholinergic drugs are two primary examples of agents in the first group.

Neuroleptics are a wide category of drugs with antipsychotic effects mainly attributed to dopamine blockade. The phenothiazine class of neuroleptics has been most implicated in heat related illness. Phenothiazines also have combined anticholinergic and central thermoregulatory effects. They inhibit afferent neuronal input to the hypothalamus, which decreases the hypothalamus's normal compensatory effect of increasing cutaneous blood flow to aid in heat dissipation.[16,17] Heat elimination is therefore reduced, leading to systemic heat alteration. Phenothiazines gained widespread use in the 1950's, and in 1954, Berti and Cima[18] published their report of lethal temperature deregulation in mice given chlorpromazine. A 1956 case report by Ayd[19] described a patients' death as a result of hyperthermia while using chlorpromazine. Since then, several other reports have described heat stroke in patients using antipsychotic medications.[3,12,20,23]

Thioxanthenes, such as zuclopenthixol, are physiologically similar to phenothiazines but their effect on heat illness has not been well studied. They are presumed to have similar effects as phenothiazines due to their structural and physiological similarities, and there is one case report of heat related illness with zuclopenthixol.[20] The dibenzapine derivatives, including clozapine, olanzapine and quetiapine, are implicated in neuroleptic malignant syndrome and increased temperature. In comparison with other neuroleptics, clozapine is not a potent dopamine (D2) receptor blocker, which is a rare but well recognized risk factor for heat intolerance in schizophrenia in hot climates.[21] However, it is a potent antimuscarinic agent and it may influence thermoregulation.[22] At present, there is only one case report of heat stroke associated with clozapine[23] in the literature and none reported with quetiapine.

Anticholinergic agents, such as atropine and benztropine have also been implicated in the impairment of thermoregulation through the inhibition of sweating and reduction in heat elimination.[3,12,20] Reports include patients receiving anticholinergic agents alone for treatment of Parkinson's or in combination with neuroleptic agents for the relief of side effects associated with neuroleptic agents.[12]

Carbamazepine can produce drug fever via immune-mediated hypersensitivity reactions. Fever can occur alone, or in the presence of dermatitis, immune complex reactions, vasculitis, or focal areas of necrosis. There is only one case report of an idiosyncratic recurrent fever in a woman receiving this as an anti-seizure medication.[24]

Our patient was at increased risk of developing heat related illness due to the concomitant use of three agents implicated in causing heat alteration. The Naranjo ADR probability scale[25] reveals a total score of only 3; a score of 0-4 is of doubtful association. It is difficult to apply the Naranjo scale in our patient given the rapid fatal outcome for our patient and therefore the inability to rechallenge or alter dosing. We strongly believe there is an association, since there are numerous previous reports for related agents and because of the severity of our patient's presentation. His work as a roofer during the heat wave certainly placed him at risk of developing a heat related illness such as exertional heat stroke. However, his presentation is much more severe than would have been expected from environmental exposure alone.

CONCLUSION

Heat stroke is preventable through protective measures from hot weather exposure but knowledge of risk factors that predispose to its development is also important. Newer antipsychotic agents are often considered safer alternatives to older, typical antipsychotics, but side effects can still occur. Physicians prescribing any type of neuroleptic or anticholinergic drug should inform their patients of the particular risks in hot environments. Dispensing pharmacists must also ensure appropriate counseling is given to the patient. Early recognition of signs and symptoms

and prompt treatment of heat related illness and heat stroke is vital and can significantly reduce the high mortality related to heat stroke.

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