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Heat Stroke and Fluphenazine Therapy: Report of a Case

Deaths coded as heat stroke or sudden heat deaths are uncommon in forensic practice, particularly in areas where heat waves are rare [*1,2*]. Where sporadic cases occur, additional risk factors are likely to be present. These include the use of certain drugs, particularly phenothiazines, anticholinergic agents, and amphetamines [*3*]. Heat stroke often pursues an extremely rapid clinical course, and investigation of fatalities may consequently become the responsibility of the medical examiner [*2*]. The phenomenon of the acute impairment of thermoregulation as a result of phenothiazine therapy is not generally mentioned in general medical reviews of heat stroke [*4,5*]. However, many psychiatrists are aware of the association, and most of the documented fatalities have been in the psychiatric literature [*6–9*]. The purpose of this paper is to report another case, with the classic findings of sudden death by heat stroke in a man with chronic schizophrenia who was on long-acting fluphenazine decanoate (Prolixin®) therapy. Environmental temperatures and relative humidity were only moderately high, demonstrating the importance of documenting the drug history and other potential risk factors in cases of this kind.

Case Report

The patient was a 21-year-old white man who had been under psychiatric care for three years with a diagnosis of chronic undifferentiated schizophrenia. He had been on high-dose phenothiazine medication: 2 g chlorpromazine (Thorazine®) a day and 100 mg fluphenazine decanoate (Prolixin®) intramuscularly every two weeks. During the last few months the dosage had been reduced to 500 mg of chlorpromazine daily and 75 mg of fluphenazine decanoate intramuscularly every two weeks. No anti-Parkinsonian or anticholinergic agents were taken, nor was there history of other drug abuse. One afternoon the patient was observed staggering outside his home, falling, and apparently striking his head. He was taken to the emergency department in coma, unresponsive, with a rectal temperature of 107°F (42°C), and severely hypotensive (blood pressure 60/30). The maximum local temperature on that afternoon was 85°F (29°C), with a relative humidity of 48% [*10*]. No definitive attempt was made to institute reduction of temperature. Cardiorespiratory resuscitation was attempted, but the patient died approximately 5 h after initial observation and 2 h after admission. Apart from a platelet count of 99 000/mm^3, the peripheral blood smear was unremarkable. The blood urea

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nitrogen was 15 mg/100 ml. The serum potassium was 6.4 mEq/litre, and sodium was 132 mEq/litre. He bled severely from all puncture sites. The case was referred to the medical examiner's office, without a definite diagnosis, in view of the possible head trauma.

At autopsy the subject was well developed and well nourished. There was no evidence of serious traumatic injury. Widespread petechial hemorrhages were prominent. The lungs were congested and edematous, and the myocardium was markedly flabby, with multiple subendocardial petechiae, most marked in the left ventricle. The brain was edematous. weighing 1620 g. There were no herniations, contusions, or meningeal hemorrhages. After two weeks of fixation, the brain was cut, revealing no contusions; however, petechial hemorrhages were focally present in the white matter. There was a small accumulation of blood (1 cm^3) in the inferior horn of the left lateral ventricle. Histologic examination of the organs revealed widespread visceral autolysis, probably more a reflection of the high agonal temperature rather than any prolonged postmortem interval. The bone marrow showed adequate megakaryocytes. There was no evidence of hepatocellular necrosis or cholestasis. In the brain, the Purkinje cells of the cerebellum were the site of unequivocal early swelling and central chromatolytic change, well demonstrated by a Nissl stain. True ischemic eosinophilic cytoplasmic alteration with nuclear pyknosis had not developed. Sections from the hypothalamus, basal ganglia, hippocampus, fronto-parietal cortex, and brainstem showed no definite pathological alterations, apart from congestion.

A general toxicology screen was done on blood and liver. Alcohol, heavy metals, barbiturates, salicylates, antihistamines, and alkaloids were specifically excluded. Ultraviolet spectrophotometry indicated the presence of a drug of the phenothiazine type. The samples were then subjected to gas chromatography for definitve identification. A peak whose retention time did not match that of chlorpromazine was obtained; a search of the files on hand did not locate a retention time under the conditions used that would match the one in question. In light of the history of fluphenazine therapy, a search of the literature was made, and the spectrofluorometric method of Smulevitch et al [*11*] was selected because of its specificity and sensitivity. The method consists essentially of hydrolysis and subsequent oxidation of the sample, after which fluorescent activity is measured at an excitation wave length of 350 nm and an emission wave length of 405 nm. The method is sensitive to 0.0002 μg per sample, with an accuracy factor of 80 to 90%.

The blood was found to contain 0.1 μg/100 ml fluphenazine, and the liver, 1.8 mg/100 ml. These levels are quite consistent with a therapeutic dosage level of the drug [*11*].

Death was certified by the medical examiner as heat stroke, with phenothiazine (fluphenazine decanoate) therapy as a contributory factor.

Discussion

This case presents many of the classic features found in acute fatal cases of heat stroke. With longer survival intervals, neuronal degeneration becomes more widespread and pronounced, although, interestingly, the hypothalamic neurones are usually not involved, showing that the impairment of hypothalamic heat-regulatory neurones by phenothiazines is biochemical, without morphological correlate, at least on routine light-microscopy [*12*]. The neuropathology is today generally thought to be determined by primary systemic effects, although Malamud et al [*13*] postulated that the cellular changes are due to direct heat effects. Edema and hemorrhages are very commonly found. In the liver, centrolobular hepatocellular necrosis, cholestasis, and portal venular dilation are also characteristic of fatal cases with longer survival [*14*]. The hyperkalemia in this case probably represents a shift of this electrolyte from the

intracellular compartment and is usually an ominous finding, whereas water depletion and hypovolemia are more characteristic of the syndrome of heat exhaustion, which is easily reversed.

When it is realized that more than 250 million patients have received antipsychotic medications in the last 20 years [*15*], it is obvious that phenothiazine-related heat deaths are sporadic. However, the true incidence is probably much underreported. Although patients on large doses are said to be more sensitive, the dosage of fluphenazine that this patient received was in the low- to mid-therapeutic range. Moreover, he had apparently not been taking the prescribed chlorpromazine. He had also recently undergone a reduction in total phenothiazine intake. Similar reductions of intake have been reported in other fatalities, underscoring the fact that this is a sporadic idiosyncratic reaction not related to true dose levels. The lack of subjective awareness of heat discomfort in these mentally disturbed patients may be an added risk factor [*8*]. The use of anti-Parkinsonian agents with atropine-like side effects, such as benztropine (Cogentin®), would appear to potentiate the induction of centrally induced phenothiazine poikilothermy, by peripheral anticholinergic depression of sweating. These drugs were not being taken by the patient. Heat stroke is at least three times more common in males than females, and this sex incidence disparity seems to apply to the drug related cases as well as as to pre-teenage children, as reported by Kumar et al [*16*], suggesting that the thermostatic center in males is inherently more susceptible to disturbance than in females.

Finally, the possibility that patients with heat stroke may fall and injure themselves quite suddenly should be remembered when head injuries are found in cases at risk.

Summary

A fatal case of heat stroke in a 21-year-old man with chronic schizophrenia is reported. Phenothiazine therapy is thought to have been a factor of major importance in the induction of this syndrome. These cases may become the responsibility of the medical examiner, and the importance of obtaining a complete drug history is stressed.

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