

## Does hyperthyroidism predispose to thioridazine-induced hyperpyrexia and cardiac arrhythmias?

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### Summary

Treatment with thioridazine resulted in hyperpyrexia and ventricular tachycardia in a young woman who was later shown to have thyrotoxicosis. The reasons why hyperthyroidism may enhance thioridazine toxicity are reviewed.

KEY WORDS: paranoid schizophrenia, ventricular tachycardia.

### Introduction

The use of thioridazine, a widely prescribed tranquillizer, is occasionally complicated by cardiac arrhythmias (Giles and Modlin, 1968; Rosenquist, Brauer and Mork, 1971; Chouinard, Ghadirian and Jones, 1978) and rarely by hyperpyrexia (Haberman, 1978; Jackowitz, 1979). We describe a young patient who suffered both ventricular tachycardia and hyperpyrexia whilst taking this drug, and suggest that hyperthyroidism, later identified in this case, may predispose to such adverse reactions.

### Case report

A 27-year-old woman was admitted to a psychiatric hospital with a 2-month history of increasing agitation and paranoid delusions. Her mental state, coupled with a family history of maternal and fraternal schizophrenia prompted a diagnosis of paranoid schizophrenia. There were no symptoms of organic illness and the only unusual clinical feature was a resting sinus tachycardia of 120 beats per min.

Her initial treatment consisted of chlorpromazine 100 mg qds increased over 10 days to 600 mg qds. On the 14th day she was given intramuscular flupenthixol 20 mg and on the 15th day chlorpromazine was replaced by thioridazine 600 mg qds because she had

developed a generalized erythematous rash. On the morning of the 18th day she was unrousable, pyrexial and was transferred to a general hospital.

On admission she reacted only to painful stimuli. The skin was hot, flushed and dry and the rectal temperature was 41°C. The pupils were dilated and reacted sluggishly to light, the limbs were flaccid and hyporeflexic and both plantar responses were extensor. The blood pressure was 80/30 mmHg and the electrocardiogram showed ventricular tachycardia.

Initial treatment consisted of lignocaine infusion, tepid sponging and cold fanning. Sinus rhythm was promptly restored and the temperature fell to normal within 8 hr. However, a further episode of ventricular tachycardia occurred 12 hr after admission and this responded to a precordial thump; there were five further self-terminating episodes of ventricular tachycardia during the next 6 hr at which time phenytoin 500 mg was administered intravenously.

Investigations including haemoglobin, white cell count, blood cultures, culture and microscopic examination of cerebrospinal fluid and urine, plasma urea and electrolytes, serum alkaline phosphatase, bilirubin and transaminases, blood gases and chest X-ray were all normal. The serum thioridazine level was 6.6 mg/l. Forty-eight hours after admission the patient was alert and answering simple questions and the only remaining abnormality was a sinus tachycardia of 110 beats per min. Thyroid function tests, performed one week later, established a diagnosis of thyrotoxicosis. Her serum T<sub>4</sub> was 200 nmol/l (normal range 50-154) and serum T<sub>3</sub> was 7.4 nmol/l (normal 1.38-3.15). Although this was satisfactorily treated with carbimazole she remained psychotic during the following 6 months.

### Discussion

Electrocardiographic changes such as QT interval lengthening and T wave flattening or inversion are common in patients taking thioridazine (Huston and

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Bell, 1966) but arrhythmias, often fatal, may also occur (Giles and Modlin, 1968; Chouinard *et al.*, 1978). Since electrophysiological studies in animals have demonstrated that these cardiotoxic effects are dose related (Yoon *et al.*, 1979), it is likely that the exceptionally high dose of thioridazine (the maximum daily dose recommended is 600–800 mg) precipitated the ventricular arrhythmias in the patient described. Their occurrence can hardly be attributed to the hyperpyrexia since they recurred several hours after the temperature had returned to normal.

Hyperpyrexia occasionally results from phenothiazine therapy but it has rarely been associated with the use of thioridazine (Jackowitz, 1979; Haberman, 1978) and its mechanism is ill-understood. The administration of chlorpromazine directly into the anterior hypothalamus of laboratory animals promotes hyperthermia (Kirkpatrick and Lomax, 1979) and the structural similarity of thioridazine to this drug suggests that the pathogenic mechanism may involve alteration in central thermoregulatory control. In addition, the concomitant use of anticholinergic agents, which inhibit sweating, may also be a contributory factor in the development of hyperthermia.

What role might thyrotoxicosis have played in this case? Thyrotoxicosis is an uncommon, although not rare, cause of psychotic symptoms (Lishman, 1978) but it is unlikely to have been responsible for the psychosis in the patient described since it did not resolve following treatment with carbimazole. However, a patient who is psychotic due to undiagnosed hyperthyroidism may be subjected to thioridazine therapy. Could such a patient be predisposed to the development of thioridazine toxicity? Certainly the enhanced thermogenesis of hyperthyroidism could promote hyperpyrexia just as the decreased basal metabolic rate in hypothyroidism predisposes to chlorpromazine-induced hypothermia (Jones and Meade, 1964). Furthermore, the known association between thyrotoxicosis and cardiac arrhythmias, and the potentiation of the cardiac effects of catecholam-

ines by thyroxine (Tse, Wrenn and Kuo, 1980), suggest that thioridazine cardiotoxicity might also be enhanced.

Unfortunately previous reports on hyperpyrexia or tachyarrhythmias during thioridazine therapy have not referred to thyroid function and we can thus only speculate on a relationship. This case illustrates the potentially fatal toxic effects of this drug, effects that may well be enhanced by hyperthyroidism.

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