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Carbamazepine and Forme Fruste Neuroleptic Malignant Syndrome

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A woman developed rigidity, autonomic instability and altered consciousness after taking an overdose of trifluoperazine and carbamazepine. A diagnosis of NMS was made despite the absence of fever, as carbamazepine might modify the presentation of NMS.

Neuroleptic malignant syndrome (NMS) is characterised by fever, rigidity, autonomic instability, and alteration of consciousness following exposure to neuroleptics (Caroff, 1980; Levenson, 1985). It is usually associated with elevation of creatine phosphokinase (CPK) levels and a leukocytosis. We report a patient who developed generalised rigidity, autonomic instability, and impairment of consciousness in the absence of fever, following an overdose of trifluoperazine and carbamazepine.

Case report

A 58-year-old married woman was admitted comatose to the acute medical wards of a teaching hospital. She was well known to psychiatric services, as she had a 27-year history of bipolar affective disorder. She had been admitted on 17 occasions in both manic and depressive episodes and had taken two previous overdoses. At the age of 21 she had developed nocturnal epilepsy which had been treated with primidone. She had subsequently been free of fits for 30 years. Before this admission she had been taking chlorpromazine (200 mg q.d.s.), trifluoperazine (10 mg t.d.s.), procyclidine (5 mg t.d.s.), and carbamazepine (400 mg b.d.; serum levels 7–8 mg/l).

She was admitted after taking an impulsive overdose of an unknown quantity of trifluoperazine and carbamazepine, which she immediately disclosed to her husband. On arrival at hospital two hours later she was in stage-3 coma. Her gag reflex was impaired, allowing the passage of an endotracheal tube without resistance, and she had bilateral extensor plantar reflexes. She was monitored overnight on the intensive care unit before being transferred to a medical ward, where she was reported to be drowsy and disorientated. She felt hot and requested a bedside fan, although her maximum recorded temperature was only 37.2 °C.

Two days after the overdose she was reviewed by one of the authors (TD) when the following signs were noted: generalised muscular rigidity, involuntary jerking movements in her face and limbs, diaphoresis, and tachycardia (120 beats/min). Her blood pressure over the previous 24 hours had fluctuated between 150/100 and 100/70 mmHg. She was disorientated in time. She was apyrexial.

Serum analysis revealed elevated CPK at 1710 IU/l (normal range up to 200 IU/l) but no leukocytosis. Renal function and liver function were normal.

All neuroleptic medication was withheld and she improved with simple supportive measures. Three days later she was fit for transfer to the psychiatric unit. She was fully orientated and apyrexial. Muscle tone was initially normal but the following day she developed cogwheel rigidity which responded to procyclidine. Her pulse was 80/min, blood pressure 140/80 mmHg, and her plantar reflexes were flexor. One week later her serum CPK had fallen to 79 IU/l. Her mental state fluctuated rapidly from sadness and self-reproach to overexcitement and irritability. Further neuroleptics were felt to be contraindicated so carbamazepine was restarted as sole treatment. Over the following week her mood stabilised and she was discharged two weeks later entirely well.

Discussion

Neuroleptic malignant syndrome typically disturbs four areas of function: temperature regulation, muscle tone, the autonomic nervous system, and level of consciousness. However, the status of partial forms remains controversial.

Levenson (1985) suggested three major and six minor criteria for diagnosing NMS, requiring all three major, or two major and four minor criteria. His major criteria are fever, rigidity, and elevated CPK, while minor criteria are tachycardia, abnormal blood pressure, tachypnoea, altered consciousness, diaphoresis, and leukocytosis. These guidelines underwrite a spectrum concept of NMS and Levenson suggests further case reports are needed. The case we describe satisfies two major and four minor criteria, and follows an overdose of trifluoperazine.

Since the diagnosis of NMS in this case is dependent on the elevation of serum CPK, other causes of this should be considered. One possibility is that since carbamazepine in overdose can induce seizures, our patient may have shown a raised CPK level following a convulsion. However, reports from her husband and nursing staff allow us to exclude this. A second possibility is that neuroleptic-induced extrapyramidal side-effects, in particular severe dystonic reactions, might themselves raise CPK levels, independent of NMS. But there are no reports in the literature of neuroleptic-induced dystonic

reactions causing raised CPK levels. A third possibility is that the overdose of carbamazepine could be responsible. There is one case report of elevation of serum CPK following a carbamazepine overdose (Bursztyn *et al*, 1987). This was associated with ataxia and nystagmus, but in that report no features of NMS were present. The CPK did not reach the extremely elevated level seen in our patient. We believe, therefore, that our patient satisfied Levenson's guidelines and that the elevated CPK may be attributed to a variant of NMS.

Three other case reports are of particular interest. Sullivan (1987) described rigidity, autonomic instability, altered consciousness, and elevated serum CPK levels in the absence of fever in a man treated with zuclopenthixol decanoate and carbamazepine. Müller *et al* (1988) described NMS with mild fever (37.8 °C) in a man treated with clozapine and carbamazepine. They suggested that as clozapine does not cause extra pyramidal side-effects it would not be expected to cause NMS, and that carbamazepine may have facilitated its development. Finally, Goldwasser *et al* (1989) reported a man with previous symptoms suggesting NMS (without fever) who developed classic NMS when treated with thioridazine. Thioridazine was discontinued and the symptoms began to resolve. Carbamazepine was commenced as sole treatment six days later. Within 24 hours the patient developed fever, fluctuating blood pressure, and elevated CPK levels, which again resolved when carbamazepine was withdrawn.

The pathophysiology of NMS is unclear, but the most popular hypothesis is of excessive dopamine-receptor blockade in the basal ganglia producing extrapyramidal symptoms, and in the hypothalamus producing fever and autonomic disturbance (Szabadi, 1984). Carbamazepine is not known to affect dopaminergic systems. It is a noradrenaline reuptake inhibitor, which probably accounts for its ability to produce dyskinesias only rarely (Evans & Gualtieri, 1985). In common with lithium it inhibits limbic kindling, reduces GABA turnover, and inhibits accumulation of cyclic adenosine monophosphate (Birkhimer *et al*, 1985). Keck *et al* (1987) have shown that there is an increased rate of NMS in those patients treated with a combination of neuroleptics and lithium. The reports of Müller and Goldwasser suggest that in conjunction with neuroleptics, carbamazepine may also facilitate the development of NMS. Perhaps the neurochemical actions it shares with lithium are responsible for this. Furthermore, we wonder if carbamazepine may modify the usual presentation of NMS, increasing the likelihood of apyrexial forms.

Adityanjee *et al* (1988) suggested that NMS should be diagnosed only in the presence of fever over 39 °C, generalised rigidity, autonomic disturbance, and altered consciousness, with raised serum CPK levels having only a supporting role. We believe that this may cause the diagnosis of NMS to be missed, with important implications for treatment. Until more is known about the pathophysiology of NMS, and further cases are reported, Levenson's guidelines would appear to have greater clinical and heuristic value.

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