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Letters to the editor

Neuroleptic malignant syndrome following tiapride treatment of clonazepam withdrawal

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There is good evidence that neuroleptic malignant syndrome (NMS) is caused by a marked decrease in the functioning of central dopaminergic neurons (Addonizio *et al*, 1987). However the idiosyncratic occurence of NMS suggests that factors other than dopamine blockade may be involved. These may include the physiological state of the patient at the time neuroleptics are administered as well as unknown metabolic factors or changes in related neurotransmitter systems. Brain cholinergic hypoactivity (Kish *et al*, 1990), an imbalance between serotonine and dopamine (Caroff and Mann, 1993) and sympathoadrenomedullary hyperactivity (Feibel and Schiffer, 1981), all have been reported to predispose to NMS. In the case we present, an acute shift in the balance of dopaminergic and GABAergic neurotransmission appears to have triggered an episode of NMS.

Case report: The patient, 73 year old woman, suffered from hypoventilation associated with kyphoskoliosis, and was hospitalised for reevaluation of her treatment (theophyline 600 mg/day). She had no history of psychiatric or neurological disease. She had been taking for at least two years 3 mg of clonazepam/day because of chronic rhumatic pain in the legs, treatment which she abruptly discontinued one or two days prior to admission.

On the seventh hospital day the patient developed confusion, disorientation, agitation, and had visual and auditory hallucinations. Over a period of thirty-six hours she received 300 mg of tiapride by intramuscular injection in divided doses.No sedative-hypnotics were given during the withdrawal period.

Approximately twelve hours after the last dose of tiapride the patient developed diffuse and severe rigidity. She was verbally unresponsive with fever (40°), tachycardia and labile hypertension (150/80 to 180/100). Laboratory results included WBC count of 19,900 and creatine phosphokinase level of 2874 U. Renal failure was present with blood urea at 21.9 mmol/l and creatinine level of 143 μmol/l. A physical examination, blood and urine culture indicated no source of infection. Tiapride was stopped immediately and the patient was treated with supportive measures only. (No bromocriptine nor dantrolene were administered). Brain scan was normal and an EEG showed nonspecific slowing.

Three days after the onset of NMS fever, state of consciousness, CPK level, blood pressure and renal function had returned to normal. WBC count and rigidity gradually became normal during the next seven days. The patient had vivid memories of her hallucinations experienced during delirium. These memories persisted for several weeks after the resolution of NMS.

In the case described herein the sequence of events suggests that the development of NMS following tiapride treatment was probably related to relative GABAergic deficiency. The clonazepam withdrawal probably caused a lack of compensatory GABAergic activation of the dopamine neurons as a normal response to the neuroleptic blockade of dopamine receptors.

Lew and Tollefson (1986) have suggested that a relative GABAergic deficiency may assume a primary pathogenetic role in NMS or may occur secondary to enhanced dopaminergic turnover. They indicate that restoration of the DA-GABA balance with GABA-mimetic agents appears therapeutic. Greenblatt *et al* (1978) reported a case of fatal hyperthermia following administration of haloperidol in a patient undergoing withdrawal from methaqualone and barbiturates. Furthermore phenothiazines exhibit dose-dependent GABA-inhibiting effects. Interestingly, this property which is not shared by all neuroleptics does not parallel the affinity for D2 receptors (Zorumski and Isenberg, 1991). These findings could help clarify the roles of neuroleptic potency and dose in the induction of NMS.

Although the mecanism responsible for NMS remains uncertain and is likely to involve complex interactions among neurotransmitters, the role of GABA in the pathogenesis of this syndrome calls for further investigation. The case we report suggests that neuroleptics should be administered only with caution to individuals whose gamma-aminobutyric acid neurotransmission is decreased (*ie*, delirium tremens).

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Electro-convulsive therapy in neuroleptic malignant syndrome

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Summary – A middle aged lady having Manic-depressive psychosis developed neuroleptic malignant syndrome (NMS) on haloperidol. The emergent psychosis after recovery from NMS resolved with judicious use of electro-convulsive therapy (ECT) followed by gradual reintroduction of antipsychotics is reported here.

Neuroleptic malignant syndrome (NMS), is a life threatening complication of central nervous system dopamine blockade. Phenothiazine and butyrophenones are most frequently implicated in this syndrome. Supportive care, discontinuation of neuroleptic drugs, and administration of bromocriptine are the keys to the management. However, after recovery from NMS, patients still remain psychotic and then the treatment of these patients poses a dilemma. Rechallenge with neuroleptic drugs carries a significant risk of recurrence of this potentially fatal condition (Well *et al*, 1988). Use of alternative drugs such as lithium (Shalev and Manitz, 1986) and carbamazapine (Peet and Collier, 1990) have been reported. Use of electro-convulsive therapy (ECT) in NMS has not been reported so far. We report a patient who developed NMS on haloperidol. The emergent psychosis after recovery from NMS resolved with judicious use of ECT and gradual reintroduction of antipsychotics.

CASE REPORT

MY, 52-year old Malay housewife, a known case of manic depressive psychosis, presented with a 2-month history of irritability, poor sleep with early morning awakening and excessive talking. Her mental status examination revealed distractability, irritability with pressure of speech and grandiosity. She was admitted and antipsychotic medications were started after excluding any organic disorder. Unfortunately, the patient refused all oral medications; hence, medications were given intramuscularly. By the sixth day she was receiving a total of 50 mg haloperidol and 200 mg chlorpromazine im/day in divided doses. On the ninth day she developed NMS. Her sensorium started to deteriorate, she was stuporous, her blood pressure dropped with postural hypotension and her body temperature increased to above 39°C. Supportive treatment was given which included intranasal oxygen and maintenance of intravenous fluids and electrolytes. The other investigations were within normal limits and not suggestive of any infection, except for mild hypoxaemia detected in the arterial blood gas and a stepwise increase in creatinine phosphokinase (CPK). The CPK levels reached a plateau of 314 $IU/_l$ over the next two days before it came gradually down.

The patient responded and returned to normal after 48 hours. Unfortunately, her manic symptoms surfaced again. In view of this, she was restarted on oral chlorpromazine 600 mg daily in divided doses, but she became stuporous again and her body temperature went up. Hence, all phenothiazines were immediately withdrawn and as she was unmanagable, ECT was started. After a course of ECT, her symptoms subsided. Later she was started on low doses of chlorpromazine.

Management of NMS has always been a problem and recently more specific treatment strategies are being tried. Among the effective drugs, dopamine agonists (amantadine, bromocriptine, carbidopa/levodopa) and myorelaxant (dantrolene) are widely used. However, the most controversial and difficult aspect of the management of NMS is rechallenge and aftercare of the patient. As psychosis is a hyperdopaminergic state, reversal of the NMS will ultimately lead to return of psychosis as evident in this patient. The rechallenge with antipsychotics has been shown to be dangerous as 70%–80% of the patients had recurrence of the NMS (Meltzer, 1973). The same thing happened to this patient thus it was decided to use ECT. However, ECT should not be used during the active NMS phase for it has been shown that there was evidence of brain oedema in autopsies of two patients who died from NMS (Stoudmoire and Lauther, 1989). However, the judicious use of ECT after the acute phase of NMS and when the psychotic picture is full blown again has more advantages than disadvantages. As seen in this patient, it was easier and faster to control the psychosis with ECT and then to rechallenge the patient with low dose neuroleptics.

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