A case of neuroleptic malignant syndrome on withdrawal of benzhexol

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Abstract

The neuroleptic malignant syndrome is a rare and potentially lethal reaction which is usually associated with the use of medications with antidopaminergic properties. This article describes the case of an elderly gentleman who developed the neuroleptic malignant syndrome after withdrawal of the anticholinergic agent benzhexol (trihexyphenidyl hydrochloride), which he was taking for Parkinson's disease. The patient improved rapidly after treatment was restarted. This case adds to the evidence that antidopaminergic agents may not be necessary for the development of this syndrome, and increased awareness of this possibility is advisable in such circumstances.

Keywords

Neuroleptic malignant syndrome, anticholinergic agent, benzhexol, trihexyphenidyl hydrochloride, Parkinson's disease

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Case report

A 74 year old gentleman suffering from Hoehn and Yahr stage IV Parkinson's disease was referred to our geriatric department for assessment and rehabilitation, complaining of worsening mobility. He was noted to have bradykinesia, mask-like facies, cog-wheeling, resting tremor and generalized rigidity. He required help with feeding, bathing, dressing and mobilisation. His past medical history was unremarkable and the rest of the examination was normal. The following were his medications at the time: benzhexol (trihexyphenidyl hydrochloride) 4mg three times daily, co-amilozide (amiloride/hydrochlorothiazide) 5mg/50mg daily, co-careldopa 220mg three times daily and citalopram 10mg daily. Since anticholinergic treatment is relatively contraindicated in this age group, we planned to replace benzhexol in stepwise fashion with the non-ergot dopamine agonist ropinirole, thereby hoping to achieve better control of his Parkinson's disease. Figure 1 shows how the medications were titrated.

Shortly after starting this switch, our patient started having episodes of dysphonia and stiffness. He deteriorated gradually over a period of several days, becoming increasingly dependent and immobile despite the use of dispersible cobeneldopa in addition to his therapy. He became sweaty and tachycardic, and was found to have a fever (38^{o}C) on two occasions. He developed lead pipe rigidity (particularly in the neck and back muscles), dysphagia, drowsiness and mutism, and became incontinent of urine. His creatine kinase was elevated (peak 1545U/L; MB-fraction 3%). His leukocytes were 8.4x10^{9}/mm^{3}, blood urea nitrogen 1.79mmol/L, creatinine 73µmol/L, sodium 125mmol/L, potassium 3.7mmol/L, albumin 39.1g/L, calcium 0.50mmol/L, bilirubin 15µmol/L, alkaline phosphatase 78U/L, alanine transaminase 47U/L, free thyroxine 16pmol/L and thyroid stimulating hormone 0.63mU/L. The ECG showed a right bundle branch block and T wave inversions in V_1, V_2, V_3 and AVR, and remained unchanged on subsequent ECGs. Although meningitis was part of our differential diagnosis, a lumbar puncture was not considered necessary because the syndrome had developed insidiously, the pyrexia had been transient and his leukocytes were normal. These symptoms developed within days of the cross-taper and conversion from benzhexol to ropinirole.

The patient was diagnosed with a mild form of the neuroleptic malignant syndrome (NMS) using Levinson's criteria.[1-6] This reaction seemed to have been a consequence of benzhexol withdrawal,[7] and his anticholinergic therapy was therefore restarted. This resulted in prompt improvement within a couple of days, and normalisation of the creatine kinase. The patient became independent with feeding again and was discharged home two months after admission. He is now able to walk with a rollator frame with minimal assistance.

Figure 1: *Dose changes of benzhexol and ropinirole (dosages apply to the cumulative dose administered over a 24 hour period)*

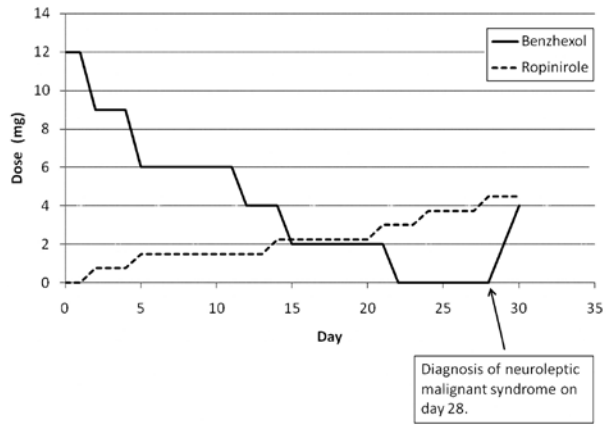
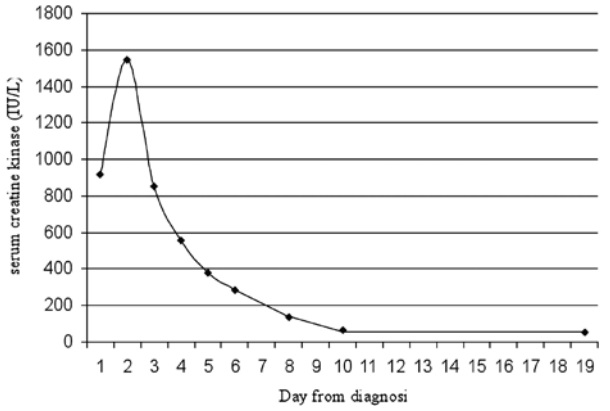


Figure 2: *Trend of creatine kinase from diagnosis day 1*



The pathogenesis of the neuroleptic malignant syndrome is unknown, but dopaminergic D2 receptor blockade in the hypothalamus and nigrostriatal track have been implicated, with altered thermoregulation and muscular rigidity respectively.[8] Some features of the neuroleptic malignant syndrome are also thought to be mediated by dysregulation of the sympathetic nervous system. Co-existing biochemical imbalances, such as hypocalcaemia in our patient, can contribute to the development of the syndrome. In cases related to atypical antipsychotic drugs, the condition is usually associated with milder degrees of hyperthermia and rigidity and the mortality is lower than with conventional antipsychotics.[9] The syndrome is complex and unpredictable, and has also been documented upon smoking cessation.[10]

Anticholinergic agents are useful in the treatment of Parkinson's disease, but are relatively contraindicated in the elderly. Advancing age is associated with an increased incidence of adverse reactions[7], probably due to the increased prevalence of conditions such as prostatic hypertrophy, dehydration, inefficiency of homeostatic mechanisms and raised intraocular pressure.

Benzhexol has a half life of one and a half hours[5], while ropinirole is known to have a large volume of distribution.[11] Our patient developed NMS during withdrawal despite a complementary increase in his dopaminergic treatment. While there is some experience with switching between different dopamine agonists,[11-13] there is no information in the literature concerning replacement of anticholinergic agents. We would not like to give the impression that anticholinergics are a routine part of the management of the neuroleptic malignant syndrome, because they may, in fact, predispose patients to hyperthermia by their inhibitory effect on sweating.[1-4, 7] In our patient, however, this reaction was precipitated by benzhexol withdrawal, and its reintroduction contributed to resolution. We advise clinicians to tail high doses of anticholinergic medications slowly, to keep patients well hydrated and nursed in a cool environment, and to be watchful for features of NMS. This episode adds to the evidence that antidopaminergic agents may not be necessary for the development of this syndrome.

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