British Journal of Psychiatry (1989), **154**, 102–104

Concomitant Treatment of Neuroleptic Malignant Syndrome and Psychosis

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Two cases are presented in which psychotic patients with neuroleptic malignant syndrome were treated with bromocriptine and thioridazine simultaneously, with a resulting control of both problems. The authors feel that this method needs further study, in the light of the potentially large number of patients at risk for these illnesses. The use of creatinine phosphokinase level as an indicator of value in NMS is also discussed.

Neuroleptic malignant syndrome (NMS) is a complex and life-threatening reaction to neuroleptic medications, thought to occur in 0.5–1% of patients receiving these drugs (Caroff, 1980). Several authors have described this disorder, and attempted to define criteria for its diagnosis (Caroff, 1980; Kurlan *et al*, 1984; Guzé & Baxter, 1985), although these are still not totally established. It appears at present that 'classic' signs of NMS include autonomic instability, fever, rigidity and altered consciousness. Protocols for treatment have been suggested (Guzé & Baxter, 1985; Mueller, 1985; Suhayl, 1987; Allsop & Twigly, 1987), with bromocriptine being the most commonly accepted remedy for patients capable of taking oral medication. ECT has also been tried with some success (Addonizio & Susman, 1987).

Few authors, however, have addressed the issue of re-treatment in previous NMS patients (Pelonero *et al*, 1985). Indeed, if it is thought that 50% of patients will redevelop NMS even when treated with 'less potent' neuroleptics (Shalev *et al*, 1985), this leaves the potential for many people to remain psychotic, with no chance at a reasonable life. It seems imperative, then, to attempt any treatment that might spare an NMS patient from being trapped in a pre-pharmacological era. We present two cases where concomitant treatment with bromocriptine and thioridazine was tried as a last resort, and met with some success.

Case reports

Case one

LL, a 32-year-old black male with a long history of schizophrenia, had been fairly well maintained on depot fluphenazine. He was initially seen approximately one year earlier by one of us (JH) when he presented with 'catatonia'. He was noted to have extreme rigidity, and difficulty with both talking and swallowing. His temperature and blood pressure, however, were within normal limits. A creatinine phosphokinase level (CPK) at that time was 1152 IU/l (normal 21-232 IU/l). He was given no further neuroleptic and was treated with bromocriptine and amantidine. The symptoms resolved rapidly, and he was discharged from the hospital non-psychotic with normal vital signs, no rigidity and a CPK of 38 IU/l. The diagnosis at this time was felt to be strongly suggestive of NMS, but was not conclusive because the 'classic' symptom of elevated temperature was absent. The patient was followed monthly as an out-patient on lorazepam, 2 mg three times a day. For eight months he remained manageable at home, with no gross evidence of acute psychosis.

He then began to suffer from auditory hallucinations and became so distressed that he was brought back to the hospital by his family. An attempt was made for five days to control his behaviour with increased doses of lorazepam, up to 2 mg by mouth every four hours. He remained paranoid and continued to talk to people who were not present. He was begun on thioridazine at 50 mg each night, while CPK values and vital signs were carefully watched. CPK values were within normal limits, at 189 IU/l prior to initiation of thioridazine and 225 IU/l after three doses. Within 48 hours he was calm, with decreased subjective distress, and a marked reduction in vocalised hallucinations. His CPK levels, however, began a steady rise with the neuroleptic, reaching 328 IU/l after four doses and 2440 IU/l after five. There were no signs of autonomic instability. Thioridazine was discontinued after the third day, and his CPK level peaked when checked 12 hours later at 6450 IU/l, 100% MM fraction. (Fractionation of CPK helps determine the various organs of its possible origin: 100% MM fraction indicates that the CPK measured is essentially all from striated muscle, a consistent sign of NMS-induced muscle rigidity.) The CPK dropped toward normal over the next three days. Unfortunately, during that time the patient was receiving no neuroleptic medication and had increasingly severe hallucinations and begged for relief; at times he became aggressive toward the staff due to his extreme fear. Increasingly large doses of lorazepam were not successful in controlling him. Pentobarbital (200 mg intramuscularly) and diazepam at 10 mg intramuscularly were also tried without success. Restraints were required on several occasions.

Carbamazepine, a drug with some antipsychotic effects (Jahn *et al*, 1984; Mueller, 1985) was begun as an alternative therapy, some six days after the thioridazine was discontinued. Once more he showed a change from a CPK which was steadily falling toward normal – even with the use of intramuscular medications and restraints prior to receiving carbamazepine – to a CPK which peaked at 1206 IU/l 24 hours after this drug was begun. Also, within this time he had a fever of up to 38.3°C (101°F) and a fluctuating blood pressure. As soon as the fever was noted the carbamazepine was stopped, and treatment with bromocriptine was again initiated at 2.5 mg by mouth

three times a day. The patient had rapid resolution of NMS symptoms but resurgence of psychosis. His CPK was normal ten days after discontinuance of the carbamazepine.

To summarise to this point, here was a patient that had a clear psychosis, who improved psychiatrically only to reveal many symptoms of NMS, and who exhibited CPK levels that rose rapidly on thioridazine and carbamazepine. We believe that this patient represents a point on the continuum of NMS patients, with some cases developing abnormal enzyme levels before autonomic instability appears. This concept of NMS as a spectrum of events rather than a single 'malignant syndrome' is also found useful by other researchers (Fogel & Goldberg, 1985; Addonizio *et al*, 1986). We feel that although the 'diagnosis' of NMS was clearly made only at the time of his fever, this patient indeed suffered from symptoms which epistemologically implied NMS on several occasions. Ten days after the carbamazepine was discontinued, and some 16 days after the thioridazine was stopped, this patient had normal vital signs and a normal CPK, but was still psychotic.

It was decided at that time, in consultation with his family, to slowly re-introduce thioridazine at 50 mg each night, while maintaining him on 2.5 mg of bromocriptine three times a day. Such concomitant therapy was intuitively decided, but we also realised that this patient had responded to bromocriptine one year earlier while he still had depot medications in his body. CPK values were monitored at least daily, and vital signs were checked at frequent intervals. The patient's vital signs remained stable, and he was significantly improved clinically after receiving three 50 mg doses of thioridazine. Following four days of concomitant treatment, the neuroleptic was increased to 75 mg at night, and after six days to 100 mg at night. He still received 2.5 mg bromocriptine three times a day as well. The patient continued a steady decrease in voiced hallucinations, and by day 5 of this regimen he was calm for the first time in two weeks. For the following four days he was no longer a management problem and continued to become more coherent.

On the tenth day of concomitant therapy, his CPK rose to 335 IU/l and his bromocriptine was increased to 5 mg three times a day. The following day revealed an enzyme level of 706 IU/l. Because of the intuitive nature of this regimen and the unknown potential for redeveloping NMS under such conditions, the trial was abandoned: note, however, that the patient showed no other signs of NMS at any time of concomitant treatment. Thioridazine was discontinued, and on only bromocriptine at 5 mg by mouth three times a day, the CPK peaked at 1671 IU/l at the check-point 24 hours later.

The patient's family decided to take him home at this stage, and he was discharged home non-psychotic and with no medication. Within one day at home and off bromocriptine he became ill and returned to the hospital. There he had a temperature of 38.6°C (101.4°F) and revealed 'classic' NMS symptoms of fever, rigidity, and autonomic instability as represented by widely fluctuating pulse and blood pressure. The diagnosis was felt to be unarguable, but further attempts to treat both the illnesses were abandoned, and only control of his physical symptoms was attempted at this time, with barbiturates. The patient was ultimately discharged to the state hospital nine days after readmission to our facility when his psychosis returned. After three months there on no medication except benzodiazepines, he was restarted on thioridazine and tolerated it well, with complete remission of psychotic symptoms. Ongoing monitoring continues, but it seems evident that this patient tolerated bromocriptine and thioridazine concurrently for almost two weeks in an attempt to keep him both non-psychotic and free from NMS symptoms. Furthermore, this patient's penchant to NMS appears to have faded with time.

Case two

EE, a 28-year-old black male with a history of several years of bipolar disorder, had been maintained for at least a year on lithium and haloperidol. He was first seen by us when he became acutely psychotic after discontinuing his medication for approximately one month. The patient was initially medicated with 10 mg haloperidol (*i.m.*), which was changed to droperidol due to his extreme aggressiveness. He received 20 mg (*i.m.*) total dose of this drug over the next four hours. Twelve hours later he was given 10 mg of haloperidol orally. Within 30 minutes of this dose (16 hours after his first dose), the patient was noted to be vomiting. We were called because the patient became diaphoretic and complained of 'feeling sick'. On examination, he was markedly rigid and diaphoretic, with a blood pressure of 160/100 and a pulse of 120. His temperature was, unfortunately, not measured at that time. All vital signs had been within normal limits three hours previously. The patient had marked cog-wheeling on passive movement of his arms. An immediate CPK was obtained, and was 5397 IU/l, 95% MM fraction.

A diagnosis of acute-onset NMS was made, and the haloperidol was discontinued. Bromocriptine was begun at 2.5 mg orally three times per day. In spite of the possible dangers associated with NMS and lithium (Ingall & Tennant, 1986), it was decided to continue his lithium at 900 mg per day, since we would be monitoring him very closely and he was very large and hostile. His CPK rose to 8022 IU/l the next morning, and fell to 4370 IU/l on the third day. During this time the patient required almost constant restraint, and at one point required 15 people to control him. It was felt that since we had had some success with the patient in case one, thioridazine could be added to his regimen, again used concomitantly with bromocriptine. This was started on day three at 50 mg at night, and after two doses it was increased to 100 mg. His CPK continued to fall smoothly, and was 355 IU/l by the seventh day after onset of NMS (i.e. after five days of concomitant treatment). His behaviour also improved, but he still remained manic and hostile. Continuing adjustment of his medications over the next 15 days led him to be ready for discharge. He was non-psychotic, quiet, calm, and co-operative. He was sent home with a normal CPK, on 1800 mg of lithium carbonate per day (level 0.8 mmol), 200 mg thioridazine at night and 7.5 mg bromocriptine three times per day. He had also given informed consent once he was stable enough to understand our treatment. At one-month follow-up the patient's CPK was 314 IU/l, at two

months 263 IU/l, at three months 345 IU/l and at four months 217 IU/l. He has remained medically stable, afebrile, and without recurrence of NMS or psychosis. Monitoring continues, and a gradual reduction of thioridazine and bromocriptine is being initiated.

Discussion

These cases seem to be a model for the 'catch-22' situation of the NMS patient. Indeed, in case one, a brief challenge with a low-potency neuroleptic threatened a resurgence of life-threatening symptoms even while the patient was improving psychiatrically. The patient in case two was physically large and aggressive, mandating effective control for the safety of both himself and the staff. The fact that changes in CPK values occurred before the onset of other autonomic symptoms allowed us to carefully watch the effects of treatment. This supports the idea that elevated CPK values are a major sign of NMS, and should perhaps be considered among the 'classic' signs of NMS (Fogel & Goldberg, 1985). Some authors have been successful in controlling psychosis in a previous NMS patient by changing the type of treatment; i.e. using an antidepressant, anticonvulsant, or ECT. We believe that the two cases presented here are the first reported where a definite NMS existed and was terminated while the patient was still being treated with antipsychotic drugs.

Although the mechanisms causing NMS are not clearly understood, it is known that bromocriptine can resolve symptoms. Here it was felt that the possible risks of concomitant use of both drugs were justified, especially since we felt confident that monitoring CPK levels often would alert us to ensuing or worsening NMS. The alternatives, after all, were few, being essentially to tie the patients to their beds until long-term commitment could be arranged.

NMS is a severe, often unrecognised complication of neuroleptic treatment. It carries a mortality rate of 20–30% (Mueller, 1985), and has an incidence of at least 1% of the thousands treated with neuroleptics each year. Experience seems to indicate that many patients will eventually tolerate antipsychotics again, although the reasons for this remain as unclear as the causes of NMS itself. Any therapy that offers a chance to treat a patient who again becomes psychotic after being diagnosed with NMS should be explored. We would also urge other clinicians and investigators to obtain a baseline CPK on all patients with prior neuroleptic treatment.

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https://doi.org/10.1192/bjp.154.1.102 Published online by Cambridge University Press