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RECOVERY AND RECHALLENGE AFTER THE NEUROLEPTIC MALIGNANT SYNDROME

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ABSTRACT

The Neuroleptic Malignant Syndrome (NMS) can have a complicated recovery and rechallenging these patients is fraught with risks of recurrence. We examined our data from a sequential case series of NMS over a four-year period for details about treatment, complications and rechallenge. Duration of NMS when treated with one versus two dopamine agonists, and neuroleptic loading rates before NMS and on rechallenge were compared using the chi-square test with correction. Duration of NMS was found to be longer when treated with more than one agonist. The mean loading rate on re-challenge, attempted in six patients, was not found to be statistically different from that resulting in NMS. However, two patients (33%) re-challenged with high-potency neuroleptics at high loading rates experienced partial recurrence. Our findings show no advantage for treating NMS with multiple agents and emphasize the need for a cautious dosing strategy while re-challenging patients with typical neuroleptics.

Key words : Neuroleptic malignant syndrome, anti-psychotic, adverse reaction

The Neuroleptic Malignant Syndrome (NMS) is a potentially fatal complication of antipsychotic medication, with reviews reporting a continued mortality of over 10% from the syndrome (Caroff and Mann,1988; Shalev et al.,1989). There is also increasing evidence that patients who recover may suffer long term neurologic and cognitive sequelae after NMS (Koponen et al.,1991; Rothke and Bush,1986). Re-challenging patients in need of maintenance neuroleptics is fraught with risks of recurrence (Shalev et al.,1986). Guidelines recommend gradual rechallenge with neuroleptics of lower potency, and no information is available in literature about the consequences should re-challenge occur with neuroleptics of similar or higher potency (Caroff and Mann, 1993). We recently published a case-control study of sequentially developing cases of NMS over a four-year period at our centre (Chopra et al.,1999). The significant finding of our study was a mortality rate that was higher than that reported in literature. In an effort to further explore the possible relevance of this finding in our context, we examined our database for information regarding complications and treatment during NMS in the patient cohort. Information pertaining to re-challenge after recovery from NMS was also analyzed.

MATERIAL AND METHOD

The study examined sequentially developing cases of NMS at the January 1, 1990 and December 31,1993. These patients were identified from Intensive Care Unit (ICU) records, where any patient diagnosed with NMS is treated. The diagnosis was confirmed using Caroff and Mann's (1993) criteria for NMS. Information about these cases was recorded on a 70-item proforma, and the neuroleptic dose was converted to chlorpromazine dose equivalents (CPZ-Eq) using the method described by Shalev and Munitz (1986).

Information pertaining to treatment, complications and re-challenge was examined for the purposes of the current study. The methodology and patient characteristics are described in detail in our earlier paper (Chopra et al.,1999). Patient subgroups were compared for mean time to recovery with treatment with one versus two dopaminergic agonists, as well as for mean loading rates at the time of developing NMS and upon re-challenge using the chi-square test with correction for small samples.

RESULTS

Thirteen patients, with a mean age of 29.5 (±9.9) years and M : F ratio of 3:1 had developed NMS during the period of the study. Five of these patients (38.5%) had a fatal outcome.

Medications used to treat the episodes of NMS are shown in table 1. The mean time to complete recovery for the patients who recovered was 13 (±7.5) days. Recovery occurred at 9 (±1.3) days when one dopaminergic agonist (amantadine or bromocriptine) had been used singly for treatment, compared to 17 (±8.4) days when two agents (both amantadine and bromocriptine) were used to treat the episode (p=0.07, NS).

TABLE 1
PHARMACOLOGICAL AGENTS USED IN THE MANAGEMENT OF THE NEUROLEPTIC MALIGNANT SYNDROME

Specific drug used	Number
Amantadine (A)	7
Bromocryptine (B)	5
L- DOPA	2
Dantrolene	3
Anticholinergic agent	2
Single Agent (A/B)	4
Two Agents (A +B)	4

TABLE 2
SHORT AND LONG TERM COMPLICATIONS SEEN IN PATIENTS WITH NMS.

Complication	Number
Short- term (N= 13)	
• Renal failure	7
• Respiratory failure	6
• Lithium toxicity	2
• Seizures	1
• Deep Vein Thrombosis	1
Long term (N= 5)	
• Psychiatric	
- Affective	5
- Memory disturbance	1
• Neurologic	3

TABLE 3
NEUROLEPTICS USED AND OUTCOME UPON RE-CHALLENGE AFTER NMS

Re-challenge (N=6)	Number
Neuroleptic used	
Haloperidol	2
Pimozide	1
Chlorpomazine	2
Thioridazine	1
Less potent than prior neuroleptic	2
Outcome	
No Complications	2
Equal or more potent than prior neuroleptic	4
Outcome	
'forme fruste' NMS	1
Severe EPS	1
No complications	2

Short and long-term complications developed by these patients are listed in table 2. Long term follow-up data was available for five of the patients who survived (63%). The mean duration follow-up was eight (range: 1-15) months. Patients were noticed to develop chronic and recurrent affective episodes different from their original illness, and neurologic complications included disturbances in muscle tone, gait and adventitious movements.

Re-challenge was attempted in six of the eight (75%) patients who recovered. Two of the six patients (33%) experienced significant side effects upon re-challenge. Drugs used for re-challenge, and the outcomes thereof are shown in table 3. The mean time to re-challenge was 74 2 days (range 2-210). The neuroleptic loading rate on rechallenge ranged from 0.04 to 1.25 CPZ-Eq/day, with a mean (± SD) of 0.46 (±0.46). This was statistically not significantly different from the loading rate preceding the NMS in these patients (Mean±SD= 0 93 ± 0.92. t=0.5, NS). Two of the four patients re-challenged with a high potency neuroleptic experienced partial recurrence of the syndrome characterized by severe extra-pyramidal symptoms (EPS) in one case and 'forme fruste' NMS, characterized by EPS and autonomic symptoms without fever in the other.

Both these patients had received neuroleptics at 'high' loading rates (0.75 and 1.25 CPZ-Eq/day).

DISCUSSION

Literature about the treatment, complications and rechallenge after NMS is scanty because the infrequency of the condition. A lot of our understanding is based on reviews (Caroff and Mann,1993) and meta-analysis (Shalev and Munitz,1986; Shalev et al.,1989) of case reports and series. Studying all cases at a centre over a period of time allows systematic examination of different aspects of the syndrome as it occurs during naturalistic treatment. Certain other important features of this study deserve mention. The cases were identified by a thorough search of elaborate ICU records. Information about the cases was collected on a detailed Proforma allowing for this closer evaluation. In addition, our study is among the few that have systematically examined rechallenge with conventional neuroleptics after NMS (Rosebush et al.,1989, Pope et al.,1991). Hence, this paper makes an important contribution to the literature about the Neuroleptic Malignant Syndrome.

Almost all patients developed acute medical complications during the episode of NMS, most frequently in the form of renal or pulmonary failure. Myoglobinuria from acute muscle necrosis and hypoxemia on blood gas analysis are described in literature as frequently occurring complications during NMS (Caroff and Mann,1993). These were also eventually the causes of death for patients with a fatal outcome (Chopra et al.,1999). This underscores the need for adequate medical supervision and management of patients when they develop NMS. The high incidence of medical problems in these patients is one indicator that the cases of NMS diagnosed were probably the most severe ones. Also, both patients on concomitant lithium therapy developed signs of lithium toxicity as well. This pattern of increased toxicity of the lithium-neuroleptic combination has also been described in literature (Spring and Frankel,1981).

Long-term complications like cognitive and neurological disturbances, noticed in our patients were similar to those described earlier in literature (Koponen et al.,1991; Rothke and Bush,1986). However, all patients for whom long-term follow-up documentation is available show the occurrence of recurrent affective-like episodes in these patients, which has not been described before. Whether this represents exacerbation of an earlier condition or the development of a new 'organic' condition is difficult to comment at this point. It is in contrast to the finding of an earlier study by Levenson and Fisher (1988) which found no change in the patient's psychiatric condition after NMS. It is likely that the patients remained in contact with health services because of these episodes, and hence information about them was available. This finding deserves closer examination.

An important finding of our study is with regard to the treatment of NMS, which in our setting was naturalistic i.e. at the discretion of the treating psychiatrist. Every patient in our series received some pharmacological intervention in addition to supportive care. However, patients treated with two dopamine agonists had a longer time to recovery than those treated with one either amantadine or bromocriptine alone. This finding calls into question the results of a recently published review (Davis et al.,2000) which found dopamine agonists to be useful in the management of NMS. It is however, similar to a related finding by Rosebush et al. (1991) where patients treated with bromocriptine or dantrolene had a more prolonged course of illness when compared to those receiving supportive care alone.

However, as this finding was difficult to explain, we re-examined our database for a possible explanation. A finding in our earlier paper (Chopra et al.,1999) was that NMS lasted about eighteen days when resulting from depot neuroleptics compared to nine days from short acting preparations. On re-examination, we found that in some instances patients developing NMS from depot neuroleptics had a protracted course, and hence had a second dopaminergic

agent added on with the hope of achieving an earlier remission. Hence, the possibility exists that a longer than expected duration of NMS was the cause why two agents were used during treatment, and not the effect However, our data does not allow us to comment about any benefit from the use of these agents. Future studies and reviews need to closely examine the question of benefit from dopaminergic agonists for the treatment of NMS in the light of such findings.

Numerous studies have demonstrated the safety of re-challenge following NMS (Levenson and Fisher,1988, Rosebush et al.,1989, Pope et al.,1991) Re-challenge was attempted in a significant portion (75%) of the patients in our series who recovered Certain significant findings also emerge from this data. A conventional neuroleptic of equal or even greater potency than the one causing NMS was used during re-challenge for four of the six patients (66%). Two of these patients for whom high neuroleptic loading rates were used developed partial recurrence of the syndrome. Hence, it appears that a combination of high potency neuroleptic administered at a rapid loading rate appears to be crucial for the recurrence of NMS on re-challenge Conversely, half the patients re-challenged with high potency neuroleptic were able to tolerate the challenge when attempted cautiously This questions the notion that only a lower potency neuroleptic should be used for re-challenge, although it would be judicious practice to use a neuroleptic of lesser potency when one is available.

The rarity and heterogeneity of the neuroleptic malignant syndrome limit the feasibility of conducting clinical trials for this disorder Any study at a single centre is likely to suffer from the limitation of a small sample size. Comparison between small samples may cause real differences to be missed (type II errors). For example, in this study, the mean loading rates on re-challenge were about half those that resulted in NMS, but the difference failed to reach statistical significance Another limitation lies in the process of case selection and the study's retrospective design. The possibility exists that milder cases of NMS were not admitted to the ICU and hence not included in the study. Nonetheless, our study raises some important questions for future investigation, and can serve to increase awareness, leading to better management of NMS.

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