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Case Report

Forced Diuresis and Expedient Blood Pressure Control in the Management of Quetiapine Induced Neuroleptic Malignant Syndrome: A Case Report

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Abstract

BACKGROUND: This case report intends to highlight the importance of safeguarding renal function from rhabdomyolysis in neuroleptic malignant syndrome (NMS) by concomitant administration of parenteral fluids at a high rate together with high doses of parenteral loop diuretics (we utilised 6 mg bumetanide daily) and tailed over a few days, in order to preserve glomerular/renal medullary perfusion and nephron function.

CASE REPORT: This case describes an elderly lady previously diagnosed with Lewy body dementia who had been started on low dose quetiapine a few days previously and presented with an acute 24 – 48 hour onset of fever, generalised stiffness, rapidly becoming uncommunicable and with high blood pressure. Haemoglobinuria was present prompting intravenous treatment with labetalol to address the BP, whereas rapid isotonic saline fluid infusions together with intravenous high dose bumetanide were instituted to safeguard the kidneys against damage due to nephron deposition, both from haemoglobinuria as well as possibly myoglobin from rhabdomyolysis. A working diagnosis of the neuroleptic malignant syndrome with secondary malignant hypertension was made, and the quetiapine withdrawn. Blood pressure was after that subsequently controlled on amlodipine, and the haemoglobinuria quickly settled within 24 hours, with large amounts of dilute urine being passed on account of the forced diuresis. The fact that renal function and creatinine kinase remained normal is testimony to how these expedient measures averted progression to both rhabdomyolysis and renal failure in this case, thereby ameliorating prognosis.

CONCLUSION: The patient was kept on infused fluids with maintenance bumetanide alone, achieving a full clinical recovery within the following 3 days.

Introduction

This case report intends to highlight the importance of safeguarding renal function from rhabdomyolysis in neuroleptic malignant syndrome (NMS) by concomitant administration of parenteral fluids at a high rate together with high doses of parenteral loop diuretics (we utilised 6 mg bumetanide daily) to preserve glomerular/renal medullary perfusion and nephron function, thereby encouraging a good urine output. It also reminds us of how blood pressure (BP) may rise inordinately in NMS and that in this situation rapid control is imperative, since high BP not only acts synergistically with rhabdomyolysis to cause renal damage but may lead to other complications, as in our case by setting up a microangiopathic intravascular haemolysis, the latter leading to haemoglobinuria which adds further insult to the nephron.

We also need to have a very low threshold of suspicion for NMS in the elderly, particularly those with degenerative neurological disease processes, who, because of their low central nervous system reserve, remain eminently susceptible to its' development.

Case Report

An 81-year-old lady with Lewy body dementia (LBD) and only on bendroflumethiazide 2.5 mg for well-controlled mild hypertension was admitted under our care, where she had been started on low dose quetiapine at 25 mg daily for behavioural symptoms one week before. Unable to volunteer any coherent history, she was noted to be rather apathetic, albeit responsive when prompted, with mild hypertonicity in

the left arm, in keeping with her LBD diagnosis. Four days later she was found febrile at 41°C, severely obtunded, completely and symmetrically stiff all over from muscular rigidity, tachycardic at 120 beats per minute and tachypnoeic at 33 breaths per minute. Other vital signs included 89% oxygen saturation on room air, while her blood pressure (BP) was around 300/160 mmHg. Upon catheterisation, the urine was clear but had a crimson hue, resembling cranberry juice. Bedside dipstick urine testing with a reagent strip immediately registered full blood, with high bilirubin, moderate protein and ketones, but negative nitrites, no leucocytes and no glucose, while the pH was 6.

Formulating a working diagnosis of the neuroleptic malignant syndrome (NMS) the quetiapine was withdrawn immediately and we set up a running intravenous (IV) saline infusion, after about one hour we administered a 6 mg bolus of bumetanide IV. The idea behind this forced diuresis being to allow the nephron to flush out any toxic products from erythrocyte and skeletal muscle breakdown. Such an intervention was intended to avert progression to renal failure, considering the very real possibility of rhabdomyolysis, compounded by the present danger constituted by intravascular haemolysis from microangiopathic haemolysis, which may be attributed to the acutely and inordinately elevated BP. High flow oxygen, was administered whereas BP was addressed via labetalol 50 mg by slow IV infusion. She was kept on IV bumetanide at 6mg daily in three divided doses while 0.9% isotonic saline infusion at a high rate (150 mLs/hour via infusion pump) was administered. Her urine output was monitored and noted to remain above 50 mLs/hour at all times.

Table 1: Laboratory findings

Blood index	*Baseline*	*Day 1*	*Day 3*	*Reference range*
White cell count (x 10^9/L)	6.4	6.7	7.5	3.5 – 11
Haemoglobin (g/dL)	9.9	10.1	10.2	11.5 – 16.5
Platelets (x 10^9/L)	227	212	217	140 – 400
Urea (mmol/L)	9.7	8.6	8.1	1.7 – 8.3
Creatinine (µmol/L)	91	82	79	44 – 80
Sodium (mmol/L)	141	139	138	135 – 145
Potassium (mmol/L)	4.7	4.3	4.1	3.5 – 5.1
eGFR (mLs/min/ 1.73 m^2)	55	61	62	
Creatinine kinase (IU/L)	104	97	99	26 – 192
Lactate dehydrogenase (IU/L)	476	337	269	140 – 280
Bilirubin (µmol/L)	35	30	27	1.72 – 17.1
Alkaline phosphatase (IU/L)	66	60	61	40 – 104
Gamma-glutamyl transpeptidase (IU/L)	23	21	24	5 – 36
Aspartate transaminase (IU/L)	17	19	17	5 – 40
Alanine transaminase (IU/L)	19	22	21	10 – 35
Haptoglobulin (mg/dL)	38	41	43	45 – 165

Following the parenteral labetalol infusion, her BP stabilised at 160/90 mmHg, and we instituted the dihydropyridine calcium channel blocker amlodipine at 5mg daily for maintenance control of blood pressure. The following day all parameters remained stable, her BP fell to 145/85 mmHg, and the IV fluids were decreased to a slower 12 hourly rate (84 mLs/hour); she continued to improve clinically, registering a full recovery of mental status to the premorbid baseline within 4 days. Subsequently, we kept her on IV 0.9% saline alternating with 5% dextrose for 5 more days, following which they were withdrawn, meanwhile, the bumetanide was tapered to 2 mg daily for maintenance treatment.

Discussion

The autonomic lability associated with NMS accrued an extremely high blood pressure (BP). In this state, damage from elevated hydrostatic pressure to the intima of arterioles causes fibrinoid necrosis within the arteriolar wall, itself triggering off the intrinsic coagulation cascade, which, in turn, results in the formation of fibrin strands, straddling the lumen like a cobweb. These slash and traumatise bypassing red blood cells (microangiopathic haemolysis) resulting in free haemoglobin which, following filtration through the glomerular sieve, impart this characteristic colour to the urine observed. Moreover, the serum haptoglobin level came back low, together with elevated lactate dehydrogenase (LDH), consistent with an intravascular haemolytic process. However, this resolved fairly quickly with the LDH returning to normal levels within 3 days.

A pre-emptive measure to prevent acute nephrotoxic tubular necrosis by induction of forced diuresis was successful, the aim of this being to wash away any haemoglobin and any myoglobin crystals that accumulate in the nephron tubule lumen. This not only discourages their precipitation out of solution, thereby safeguarding luminal patency, but also reduces contact time of these toxic products with the basolateral tubule membrane, insofar that damage is minimised and a rapid re-establishment of physiological exchange mechanisms is promoted. Prognosis in NMS worsens significantly with the onset of renal failure. In our case, the pigmented urine cleared within 24 hours of starting the rapid saline infusion and blood pressure responded well to the nonspecific α/ß blocker labetalol, also readily returning to within normal range following its administration. All this, together with the fact that the serum creatinine kinase (CK) failed to rise, are positive prognostic indicators that rhabdomyolysis has been effectively averted and bode well for a quick and full recovery.

Autonomic instability is inherent to NMS insofar that both low and high blood pressure (BP) may occur; indeed there may also be rapid fluctuations in it throughout this state. However, in our case, the BP was sufficiently high to present an additional clinical adverse factor (which, if left unaddressed, may have led to malignant hypertension) being severe enough to have already initiated microangiopathic haemolysis (as attested by the low haptoglobin and isolated hyperbilirubinaemia), with subsequent haemoglobinuria (highly positive blood marking on the urine reagent strip) presenting the real possibility of compounding any nephron damage in the event of

rhabdomyolysis. Such a high BP risked causing other macrovascular complications such as acute stroke, myocardial infarction, retinal disease and acute renal failure. It followed that aggressive control of this added complication must be taken as seriously as the management of the NMS itself and was indeed crucial to ensure a positive outcome. On the other hand one must also be weary of low BP in NMS (in view of the autonomic lability) such that close BP monitoring is mandatory, so that drops in the BP may be countered with increased IV hydration to safeguard end organ perfusion (whilst withdrawing any BP lowering medication).

Literature review

Second generation antipsychotics (SGAs) or atypical antipsychotics have been known to result in correspondingly 'atypical' NMS where the classical features are altered. Traditionally NMS has been postulated to originate from central dopaminergic D1 and D2 receptor blockade, leading to muscle rigidity and thermogenesis. In fact frequency of NMS incidence was found to be proportional to the potency of dopamine blockade in the mesocortical, mesolimbic, nigrostriatal and hypothalamic tracts [1]. However atypical antipsychotics function more via serotonergic 5HT and adrenergic receptor blockade, bearing little or no central antidopaminergic activity. Quetiapine has been demonstrated to produce an NMS variant where autonomic manifestations (tachycardia, tachypnea, diaphoresis, BP fluctuations) seem to predominate over extrapyramidal symptoms (EPS); this has been attributed to the noradrenaline reuptake inhibition, histaminergic antagonism and serotonin toxicity that feature in quetiapine pharmacology [2] [3]. SGA induced NMS (SGA-NMS) has been shown to be somewhat more benign than the first generation antipsychotic (FGA) subtype, carrying a mortality of 3% for SGA, as opposed to 16.3% for FGA induced NMS [4]. However, when outcomes of SGA - NMS were compared amongst the different individual, causative atypical antipsychotics, quetiapine was associated with the highest fatality rate at 7.7%, together with the lowest complete recovery rates (61.5%), despite carrying the least tendency towards EPS [5]. In this latter finding it was comparable only to clozapine where NMS cases occurred in the total absence of hypertonicity or rigidity, however, the other main features of NMS (fever, CK rise, autonomic dysfunction) remain ubiquitous amongst both FGA and SGA induced forms [6] [7] [8].

Review of case reports has demonstrated that SGA - NMS may occur equally with atypical antipsychotic monotherapy, as well as in combination with other psychoactive drugs [1]. Specifically, quetiapine has been implicated in NMS when combined with the likes of venlafaxine [9] [10], fluvoxamine [11], other antidepressants [1] and sulpiride [12]; paradoxically, however, quetiapine has also incurred NMS when associated with muscle relaxant drugs such as benzodiazepines and valproate [1]. Additionally, it has also been reported with lithium [1] and with antiparkinsonian drugs in a case report which led to a fatal outcome [13]. In this respect, the fact that antidepressants, lithium and other mood stabilisers may precipitate NMS, in combination with antipsychotics, led to the hypothesis that the serotonin excess they produce could determine a 'relative hypodopaminergic state' such that this serotonin - dopamine disequilibrium favours NMS [14] [15]. One study even reports onset of NMS purely on the administration of an SSRI (selective serotonin reuptake inhibitor) combination, in the absence of dopamine inhibition [15].

The fact that quetiapine-induced NMS is completely idiosyncratic has been demonstrated in many studies, whereby it has been shown to occur equally with patients on steady-state doses of the drug without fluctuations, as well as when another psychoactive drug is introduced, or with dose titration of quetiapine [8]. Cases had occurred after patients had been many months stable on a fixed dose regimen of quetiapine, who before the onset of NMS had their primary psychiatric condition well controlled and who did not display any previous history of drug-induced EPS [8]. Around 50% of NMS cases occurred with patients on stable doses of SGAs in another study considering all atypical antipsychotics across the board, whilst 60% of those cases of SGA - NMS (including participants on both steady state as well as recently altered doses of atypical antipsychotics) were on some other concomitant psychotropic medication [16]. However, certain epidemiological factors did emerge that effectively rendered one more susceptible to quetiapine-induced NMS [9] [17] [18] namely: males are twice more likely than females, age range of between 20 – 50 years and mental impairment or learning disability. Other pharmacological and pathophysiological factors were also implicated in increasing the likelihood of NMS with patients on antipsychotics in general [19] [20] [21]: history of previous NMS, rapid dose escalations, intramuscular depot antipsychotic injections (particularly upon dose increase), high potency neuroleptics, states of decreased absolute or effective circulating blood volumes, such as dehydration, third spacing, sepsis or other states of shock, and catabolic states such as malnutrition.

Our case description presents underlying cognitive impairment as the sole risk factor; however, we argue that such elderly patients, particularly those with cognitive impairment, remain relatively more susceptible to the development of NMS compared with the general population. This challenges the commonly held belief that NMS occurs mostly in younger schizophrenic patients [22] and that presence of dementia seems to confer a degree of 'immunity' from the syndrome. One must bear in mind that old age brings about with it an increased permeability of the

blood-brain barrier and a lower threshold for neurotransmitter decompensation (lower neural mass, together with a decreased enzymatic degradation of psychoactive drugs and neurotransmitters at the synaptic level); additionally a lower hepatic metabolism rate and renal clearance rate, a lower lean muscle mass and increased fat to water ratio are all pharmacokinetic factors that potentiate the predicted effect of psychoactive drugs [23]. Moreover, Lewy body dementia is notorious for its associated neuroleptic sensitivity, which is potentially fatal and afflicts 50% of LBD patients [24]. As such we believe that this case is a reminder to the clinician that geriatric cases, particularly those with heightened sensitivity to neuroleptics as with LBD, remain eminently susceptible to not only the 'extrapyramidal' or striatonigral manifestations, but also to the other central manifestations of dopamine blockade, as resultant from neuroleptics, with the former giving rise to parkinsonism, whilst the latter to NMS.

In conclusion, we wish to highlight how the strategy adopted above of forced diuresis with expedient BP control seems to be successful in promoting a positive outcome with NMS patients. We also suggest that any elderly who already have some form of extrapyramidal dopamine insufficiency state (idiopathic or drug-induced parkinsonism, LBD, Parkinson plus syndromes) ought to be earmarked for the other central dopamine deficiency complications, namely NMS, thereby lowering the clinicians' threshold of suspicion further in such cases.

Learning points: NMS is often subacute and presents insidiously a low suspicion threshold is needed for NMS in an elderly on antipsychotics who presents with psychomotor retardation or deterioration; cognitive impairment, particularly LBD, presents an additional risk factor for NMS. The usual features of NMS may be lacking in cases induced by atypical or second-generation antipsychotics (SGAs); early treatment is crucial in safeguarding against renal damage where BP must be closely monitored, and both excessively high or low values treated accordingly, since prognosis improves in cases where rhabdomyolysis has been averted or minimized.

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