

•Case report•

Neuroleptic malignant syndrome in a patient treated with lithium carbonate and haloperidol

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Summary: A 39-year-old female with a 20-year history of bipolar disorder was admitted due to a recurrence of a manic episode with psychotic symptoms. She was treated with standard doses of lithium carbonate and clozapine. Three days after admission, she showed aggressive behavior and refused to take her medications so her oral clozapine was switched to intramuscular haloperidol. Three days later she developed a high temperature and exhibited symptoms of neuroleptic malignant syndrome (NMS) including excessive sweating, cramps and tremors in limb muscles, muscle rigidity, and impaired consciousness. The haloperidol and lithium were stopped immediately, symptomatic treatment was provided, and she was administered the dopamine agonist bromocriptine. The NMS symptoms resolved within three days but she continued to have severe psychotic symptoms. She was subsequently re-challenged with valproate and olanzapine but the NMS did not re-occur. After one month of this treatment she recovered and was discharged. Several case histories similar to this one suggest – but do not prove – that individuals concurrently receiving lithium and antipsychotic medications may be at higher risk of developing NMS than those receiving monotherapy with antipsychotic medication.

Key words: lithium carbonate; haloperidol; neuroleptic malignant syndrome; China

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1. Case history

A 39 year-old female was admitted to our hospital on 18 February 2014 with a three-day history of agitation, elevated mood, and paranoia. She had a 20-year history of manic and depressive episodes that included four previous psychiatric admissions. During the previous admission at our hospital, she was treated with clozapine, risperidone, and lithium carbonate (maximum dosage 1.0g/day) and given a one-time injection of haloperidol 5mg. After discharge, her dosage of lithium carbonate was gradually reduced to 0.25g/day. In September of 2013, she vomited repeatedly and was diagnosed with 'sinus thrombosis' at a local hospital where she recovered after inpatient treatment. No other physical condition or family history of mental disorders was reported.

Routine physical and neurological examinations at admission found no abnormalities. Her routine blood tests, biochemical tests, electrocardiogram, and electroencephalogram were also normal. She was diagnosed with bipolar disorder, current manic episode

with psychotic symptoms, based on criteria specified in the *International Classification of Diseases, 10th edition* (ICD-10).^[1]

During the first three days of admission, she was treated with lithium carbonate 0.75g/day and clozapine 150mg /day (starting at 50mg/day and gradually increasing). On the third day of admission she became more agitated, argued with nurses, refused to take her medication, and became aggressive. Based on this change, her antipsychotic medication was changed from oral clozapine to intramuscular haloperidol (5mg bid) and scopolamine (0.3mg bid). Three days later she became disoriented and experienced cramps and tremors in her limb muscles, increased muscle tone, excessive sweating, and intermittent visual hallucinations. She had a fever of 38.5 - 39.6°C but there was no evidence of infection. Her white blood count was $15.6 \times 10^9/L$ with 86.1% neutrophilic granulocytes. Electrolyte levels were normal and serum lithium level was 0.61mmol/L. Chest X-ray showed no abnormalities. Electrocardiogram showed a nodal tachycardia of 106 beats per minute.

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Based on a probable diagnosis of Neuroleptic Malignant Syndrome, her lithium, haloperidol, and scopolamine were stopped. She was given intravenous penicillin and supportive care to maintain her fluid and electrolyte balance. After consultation with senior clinicians her diagnosis was confirmed as NMS and she was treated with the dopamine agonist bromocriptine (2.5mg tid). Over the next two days her temperature dropped to normal and her physical symptoms subsided, though her psychotic symptoms remained. Given the severity of her psychosis, she was cautiously re-introduced to medications using 1.0g/day valproate as the mood stabilizer, olanzapine as the antipsychotic (up to a maximum of 20mg/d), and a variety of nighttime sleep medications (lorazepam, alprazolam, clonazepam, and clonazepam). Her symptoms gradually resolved and she was discharged on 28 March 2014, after six weeks of inpatient treatment.

2. Discussion

The diagnostic criteria for neuroleptic malignant syndrome (NMS) provided in the fourth edition of the American Psychiatric Association *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV)^[2] specify that the individual must exhibit severe muscle rigidity and elevated temperature associated with the use of antipsychotic medication and have at least two of the following associated symptoms: (a) diaphoresis, (b) dysphagia, (c) tremor, (d) incontinence, (e) changes in level of consciousness ranging from confusion to coma, (f) mutism, (g) tachycardia, (h) elevated or labile blood pressure, (i) leukocytosis, or (j) laboratory evidence of muscle injury (e.g., elevated CPK). NMS is usually seen at the beginning of antipsychotic treatment (within a week). In our case a patient who was already taking clozapine and lithium developed muscle rigidity, fever, tremor, sweating, altered consciousness, and leukocytosis 3 days after changing the clozapine to haloperidol. Despite our inability to confirm the diagnosis by assessing muscle enzyme levels (due to lack of the required laboratory facilities), the history and symptomatology were sufficient to meet the DSM-IV criteria of NMS.

First described by Delay in 1960,^[3] NMS is considered the most severe side effect of antipsychotic medications. It is uncommon, currently occurring in only 0.01 to 0.02% of patients treated with antipsychotic medications, but it has a high case-fatality rate of 10%.^[4] Almost all dopamine antagonists have been associated with NMS, but the risk of NMS appears to be greater when using high-potency conventional antipsychotics (such as haloperidol) than when using low-potency or atypical antipsychotics.^[4] NMS has also been reported in patients taking lithium^[5] and antidepressants.^[6]

Lithium, particularly in high doses, is also associated with neurotoxicity^[7,8] so it is reasonable to suggest that individuals concurrently taking lithium and neuroleptic medications – a substantial minority of individuals

with manic phase bipolar disorder – are at greater risk of developing NMS than those taking antipsychotic medications without lithium.^[9] There are multiple case reports of NMS occurring in individuals simultaneously receiving antipsychotic medication and lithium.^[10,11] The case described in this report is an example in which a person already taking clozapine and lithium developed NMS after the clozapine was changed to haloperidol, a high-potency traditional antipsychotic medication. The case supports the contention that lithium may increase the risk of NMS associated with the use of high-potency antipsychotics, but in the absence of a comparison group (e.g., lithium + haloperidol versus monotherapy haloperidol) no definitive conclusion can be drawn. Such case reports are not sufficient to prove the case that individuals taking lithium plus antipsychotic combinations are at greater risk of NMS than those on monotherapy antipsychotic medication; the outcome event (NMS) is so rare and the potential confounding factors (age, physical health, dosage, rate of change of dosage, etc.) so many, that impossibly large sample sizes would be needed to definitively resolve this issue.

The mechanism of NMS is entirely unclear. Most researchers^[12,13] believe that the non-infectious hyperthermia seen in NMS is related to disruption of dopamine receptors in the hypothalamus; that hyperfunction of the sympathetic nervous system (manifested as tachycardia, polypnea, hypertension, sweating, etc.) is the result of the dopamine antagonists' effects on the function of the autonomic nervous system; and that obstruction of dopamine receptors in the striatum results in muscle rigidity, tremor, and the catabolism of voluntary muscles (leading to myoglobinuria and increased serum creatine kinase).

The outcome of NMS is related to age, the physical condition of the patient, and on whether or not NMS is detected early.^[4] Fatalities are more likely to occur in cases where the individual is elderly or physically frail, and where the condition was not recognized early (so the medications were continued even while the symptoms worsened). The overall principle for the treatment of NMS is the immediate cessation of antipsychotic medication, provision of supportive treatment (i.e., maintaining fluid balance, cooling, and prevention of infections), and, if necessary, administration of dopamine agonists such as amantadine, L-dopa, or bromocriptine. Recurrence of NMS in patients re-challenged with antipsychotic medications occurs in about 30% of cases. It is generally recommended that clinicians wait for at least 20 days prior to re-challenging a patient who has experienced NMS,^[4] but in some cases where the psychiatric symptoms are severe – as in this case – it may be necessary to shorten this re-challenge interval.

Conflict of interest

The authors report no conflict of interest related to this manuscript.

Informed consent

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碳酸锂结合氟哌啶醇致恶性综合征

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概述: 一名 39 岁的女性双相障碍患者因再次出现伴精神病性症状的躁狂发作而住院, 总病程 20 年。用常规剂量的碳酸锂和氯氮平治疗。入院 3 天后, 患者出现攻击行为, 并拒绝服药, 因而停用氯氮平口服, 予氟哌啶醇肌注。3 天后, 患者出现高热以及其他恶性综合征的表现, 如大量出汗, 肢体肌肉痉挛、震颤, 肌强直以及意识障碍。立刻停用氟哌啶醇和锂盐, 对症支持治疗, 同时用多巴胺激动剂溴隐亭治疗。恶性综合征的症状在 3 天内缓解, 但精神病性症状依然很严重。继而使用丙戊酸钠和奥氮平治疗, 未再出现恶

性综合征。又治疗 1 个月后, 患者康复出院。过去有若干个病例也与此类似, 这些病例提示抗精神病药物合并锂盐治疗引起恶性综合征的风险可能比单用一种抗精神病药物要高。当然病例报告本身无法证实这一点。

关键词: 碳酸锂; 氟哌啶醇; 恶性综合征; 中国

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