Psychopharm

Journal of Psychopharmacology
19(4) (2005) 422–425

ISSN 0269-8811
SAGE Publications Ltd,
London, Thousand Oaks,
CA and New Delhi
10.1177/0269881105053310

Neuroleptic malignant syndrome due to three atypical antipsychotics in a child

Dong-Seon Chungh *Division of Child and Adolescent Psychiatry, Department of Psychiatry, Seoul National University Bundang Hospital, Seoul, Korea.*

Boong-Nyun Kim *Division of Child and Adolescent Psychiatry, Department of psychiatry, Clinical Research Institute, Seoul National University Hospital, Seoul, Korea.*

Soo-Churl Cho *Division of Child and Adolescent Psychiatry, Department of psychiatry, Clinical Research Institute, Seoul National University Hospital, Seoul, Korea.*

Abstract

Neuroleptic Malignant Syndrome (NMS) is a rare, potentially fatal and idiosyncratic drug reaction. It is characterized by a sudden loss of body temperature control, renal and respiratory failure, muscle rigidity, loss of consciousness and impairment of autonomic nervous system. Although NMS was previously associated with the use of classical high-potency neuroleptics, cases have started to emerge with atypical neuroleptics. This article discusses the first case of NMS in a child, induced by the use of risperidone, olanzapine and quetiapine.

Keywords

neuroleptic malignant syndrome, risperidone, olanzapine, quetiapine

Introduction

Neuroleptic Malignant Syndrome (NMS) is a rare, potentially fatal and idiosyncratic dose-independent drug reaction (Shalev and Muniz, 1986). It is associated with a sudden loss of body temperature control during drug therapy, resulting in a rise in body temperature that can be fatal (within 24 to 72 hours), due to consequent renal and respiratory failure, muscle rigidity, loss of consciousness and impairment of the autonomic nervous system (Shalev and Muniz, 1986). The pathogenesis has not been well-known until now, but NMS is thought to be mediated primarily by dopaminergic blockade (Tsai *et al.*, 1995). Although NMS can occur with every kind of antipsychotics, atypical antipsychotics and a relatively new antipsychotic agent with potent antiserotonergic activity and less anti-dopaminergic activity, it was expected that NMS could occur as a complication of atypical antipsychotic therapy less frequently (Bajjoka *et al.*, 1997). However, atypical antipsychotics-induced NMS has to be approached more cautiously because it has atypical features which can be misdiagnosed or underdiagnosed. The literature on NMS and atypical antipsychotics includes mostly case reports and occasionally case series (Hasan and Buckley, 1998). The two most comprehensive reviews discussed data-related to clozapine or risperidone (Kara gianis *et al.*, 1999). Until now, most cases with atypical antipsychotics-induced NMS were reported among adults. To our knowledge, this is the first case of NMS in a child that has occurred through the use of risperidone, olanzapine and quetiapine.

Case report

A 12-year-old girl diagnosed with bipolar disorder not otherwise specified (NOS) and mild mental retardation, was hospitalized due to aggressive and violent behaviours. Prior to the admission, she had been diagnosed with Attention Deficit Hyperactivity Disorder (ADHD) and treated with methylphenidate. She was evaluated using Intelligence Quotient (IQ) by Wechsler Intelligent Scale for children (WISC). Full-scale IQ was 68. Her father, who had suffered from major depressive disorder with psychotic features, committed suicide when she was 3 years old.

Upon initial evaluation, the patient's physical condition and her laboratory findings were within normal limits. She had no pubertal changes and her Tanner's stage was 1. We started with risperidone 1.5 mg and carbamazepine 400 mg orally to control aggression, mood instability and violent behaviours. Carbamazepine induced skin rashes, so the drug was discontinued. Instead of carbamazepine, valproic acid 450 mg was added in the hope of mood stabilization.

On the twenty-fifth day after risperidone (2 mg/day) administration, high fever (39 °C), myalgia and throat infection suddenly

Corresponding author: Soo-Churl Cho, Division of Child and Adolescent Psychiatry, Department of Psychiatry, Clinical Research Institute, Seoul National University Bundang Hospital, 28 Yungundong, Chongrogu, Seoul, Korea. Email: soochurl@snu.ac.kr

developed. Her chest PA, CBC with differential count and urine analysis with microscopic examination were within normal limits. Then acetaminophen 300 mg was administered to the patient because of a suspicion of acute pharyngotonsillitis.

On the twenty-ninth day after risperidone (2 mg/day) administration, her high fever (39 °C) hadn't subsided. Her mental status was stuporous and she became lethargic. We started fluid infusion due to her poor oral intake. Her vital signs included blood pressure at 90/60, pulse rate at 108/min and respiration rate at 32/min. She displayed hypotension, tachycardia and tachypnea. At that time, laboratory findings showed the following values: creatinine phosphokinase (CPK)-701 IU/L (normal range 20–270), CPK-MB-23 U/L (normal range 0–16 U/L), lactic dehydrogenase (LDH)-360 IU/L (normal range 100–225), GOT/GPT (70/101) and WBC count in CBC (11,210/mm^3). Toxicology screen and blood culture were negative. Urinalysis, chest radiograph, lumbar puncture and serum electrolytes were unremarkable. Brain MRI revealed atrophic change in cerebellum. The above symptoms did not account for viral and bacterial infections due to negative blood culture and spinal-tapping findings. They were not thought to be the result of pharyngotonsillitis because conservative treatment was not effective and mental status became stuporous increasingly. Clinical features of her signs and symptoms were compatible with NMS by DSM-IV criteria. She was taken off all psychiatric medications including risperidone. Ibuprophen syrup and intravenous fluids were administered for muscle discomfort, fever and maintenance of normal renal function. Two days later, her body temperature fell to within the normal range. She became alert. However, laboratory data of CK (794 IU/L), CPK-MB(27 U/L) and LDH(397 IU/L) showed higher than normal values.

On the fourth day after the withdrawal of risperidone, general conditions including vital signs recovered rapidly. CPK-MB was decreased to 17 U/L. At that time she displayed severe violent and aggressive behaviours without mental confusion, so we restarted olanzapine 2.5 mg and valproic acid 150 mg orally, due to the aggression and mild mood fluctuation.

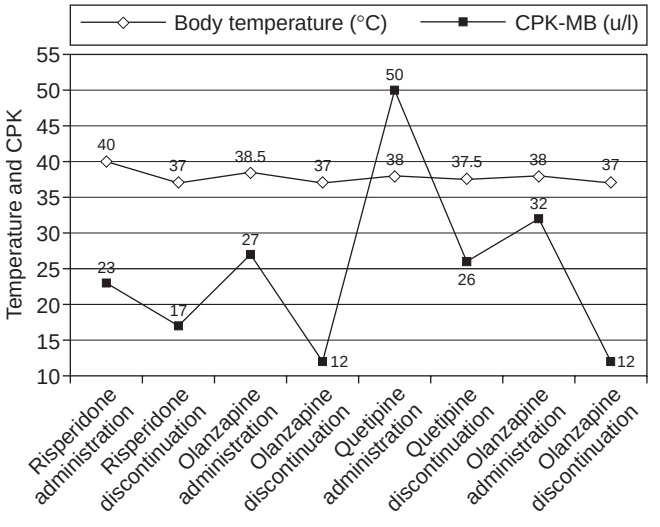

Figure 1 Serial Patterns of the level of body temperature and CPKMB atypical antipsychotics administration

On the second day after olanzapine (2.5 mg/day) administration, the patient's temperature was elevated to 38.5 °C again. Physical examinations including mental status were unremarkable. Laboratory findings showed abnormally high values such as CPK (750 IU/L), CPK-MB (27 U/L), LDH (320 IU/L), GOT/GPT (31/54). Her abnormal laboratory findings and fever were thought to be the early manifestations of olanzapine-induced NMS, so olanzapine was discontinued.

On the second day after the withdrawal of olanzapine, fever was subsided to 36.5 °C. All the abnormal laboratory findings were normalized. Her symptoms of violent and aggressive behaviours, however, could not be controlled by valproic acid despite full dose administration. She was placed under physical restraint all day because of violent behaviour. Quetiapine 25 mg was administered orally to control severe impulsivity and violent behaviours without full washout period. Quetiapine dosage was increased to 75 mg in a week along with valproic acid simultaneously.

On the third day after quetiapine 75 mg administration, she again developed a high fever (39 °C), but without URI symptoms. Physical examinations including mental status were unremarkable. However, the laboratory findings became abnormal: CPK (2299 IU/L), CPK-MB (50 U/L), LDH (449 IU/L). These were also thought to be signs of quetiapine-induced NMS, so the quetiapine was discontinued.

On the third day after quetiapine discontinuation, lithium 150 mg and valproic acid 600 mg orally were restarted twice a day for emotional instability and violent behaviours. The patient had been prescribed lithium 900 mg and valproic acid 960 mg daily until 120 days after her admission. But her main problems, such as impulsivity and aggressiveness, persisted despite continuous medication.

On the sixty-ninth day after lithium and valproic acid administration, olanzapine 2.5 mg orally was restarted for her behavioural problems along with lithium and valproic acid because only lithium and valproic acid were not effective on emotional instability and severe impulsivity.

On the fourth day with olanzapine 2.5 mg re-administration, the patient's temperature was elevated to 38 °C again. The laboratory findings, which were correlated with NMS, became abnormal, such as CK(1345 IU/L), CPK-MB(32 U/L), LDH(571 IU/L). These findings were thought to be olanzapine-induced NMS. Therefore, olanzapine was discontinued.

On the thirtieth day after olanzapine discontinuation, as three atypical antipsychotics induced NMS, she showed more aggressive and violent behaviour. She complained of pain and bad physical conditions due to the physical restraints imposed. We were not able to administer any adequate anti-psychotics due to three atypical anti-psychotic-induced NMS episodes. We decided to apply electroconvulsive treatment (ECT) to this patient (two sessions/week) in order to control aggression, violent behaviour, and mood instability.

After the third trial of ECT, her impulsivity and violent behaviours began to improve markedly. She showed good condition because of ECT-maintenance treatment.

After a total of eight ECT treatment sessions, valproic acid was restarted at 320 mg daily and increased to 760 mg with daily monitoring of drug level. She was able to be discharged with controlled behaviour problems and received regular out-patient treatment with valproic acid only.

Discussion

NMS is an increasingly recognized acute reaction, which can occur either in response to administered dopamine receptor blocking agents or to withdrawal of dopaminergic drugs (Keyser and Rodnitzky, 1991). The principal features of NMS due to atypical antipsychotics are autonomic instability, extrapyramidal symptoms (EPS) and hypothermia. Typically, the first sign is severe skeletal muscle rigidity, followed by progressive pseudo-parkinsonian features such as bradykinesia, tremors and masked faces. Changes in mental status can occur within 1 to 3 days and may progress to stupor and even coma in severe cases. Other features include fever, profuse diaphoresis, tachycardia, tachypnea, labile blood pressure and urinary incontinence or retention. Pertinent laboratory abnormalities include increased serum sodium due to water depletion, leukocytosis and the increase in serum CK and other muscle enzymes (Knezevic *et al.*, 1984). As many as 16% of cases of NMS begin within 1 day of therapy and 30% within 2 days (Caroff and Mann, 1988). NMS has been estimated to occur with a frequency of 0.02 to 3.23% and to occur either more commonly in men or about equally between genders (Caroff and Mann, 1993).

The mortality associated with NMS has been constantly declining, with an incidence of 76% in the 1960s, 22.7% in the 1970s and 14.9% in the 1980s (Kellam, 1987). Because this is still a high mortality rate, it is important for clinicians to watch for early signs and symptoms of NMS. NMS may be misdiagnosed because of misattribution of the signs and symptoms to underlying psychiatric illness, acute infectious process, Parkinson's disease, delirium or dementia (Webster and Wijeratne, 1994). Another difficulty in diagnosis of NMS is its similarity to serotonin syndrome. Serotonin syndrome produces behavioural or cognition abnormalities, autonomic nervous system dysfunction and abnormal neuromuscular activity, all of which closely resemble NMS. A main differentiating feature is that neuroleptic agents most commonly induce NMS, whereas serotominergic agents, including antidepressant agents, most commonly induce serotonin syndrome (Mills, 1993). Because NMS is mediated by antidopaminergic action, it was expected that atypical neuroleptic agents would not cause dystonia or NMS owing to its unique mechanism of action with attenuated antidopaminergic activity and more potent antiserotonergic activity (Knezevic *et al.*, 1984). There are a few childhood and adolescent-onset NMS cases (Pearlman, 1986; Addonizio and Susman, 1987). The findings reported in juvenile NMS bear striking similarities to those reported in the adult population (Steingard *et al.*, 1992). Fever, rigidity, altered mental status and tachycardia were observed in more than 70% of cases and symptoms followed exposure to neuroleptic medication (Steingard *et al.*, 1992). In 20% of the cases, there was evidence of pre-existing abnormal brain function, either in the form of mental retardation or EEG findings, like this case (Latz and McCracken, 1992). The new antipsychotic agents that have come into use over the past decade – clozapine, olanzapine, risperidone, quetiapine and ziprasidone – may be distinguished from their predecessors by their ability to alleviate psychotic symptoms with minimal-to-no extrapyramidal side-effects (Donna *et al.*, 2000). But any atypical neuroleptic agents can cause NMS, including the atypical neuroleptics clozapine, olanzapine, risperidone and possible quetiapine (Bajjoka *et al.*, 1997; Filice *et al.*, 1998; Stanley and Hunter, 2000). In 1992, risperidone became the second proposed atypical antipsychotic to be introduced in the USA. A benzisoxazole, risperidone is chemically unrelated to the benzepines clozapine, olanzapine and quetiapine (Tarshy *et al.*, 2002). Because of its high affinity for 5-HT_{2A} receptors, it was anticipated that, similar to clozapine, risperidone might be an effective antipsychotic with a low incidence of EPS (Tarshy *et al.*, 2002). Over 20 cases of NMS have been reported to be associated with risperidone until now. Of these cases, three were geriatric patients (over 65) and no paediatric case has been reported. For most of the cases, risperidone-induced NMS occurred from 12 h to 23 days after the initiation of risperidone therapy. Major manifestations of risperidone-induced NMS were muscle rigidity, high fever, dysfunction of autonomic nervous system, altered conscious level and elevated serum CPK level (Bajjoka *et al.*, 1997).

Olanzapine was the third atypical antipsychotic drug approved in the USA in 1996. It is structurally similar to clozapine. Olanzapine is more atypical than risperidone pharmacologically in that it does not cause significant prolactin increase or acute dystonic reactions in humans (Stewart, 2002). An important difference with other atypical antipsychotics relates to dopamine receptors (Beasley *et al.*, 1997). It is a potent antagonist of D2 and has somewhat less affinity for D1 and D4 dopamine receptors (Jibson and Tanson, 1998). In addition, it has a high affinity for histamine H1, muscarinic M1 and alpha-noradrenergic receptors. More significantly, it blocks 5-HT2A receptors to a greater degree than dopamine D2 receptors allowing for a high 5-HT/D2 ratio (Bymaster *et al.*, 1996). There has been more than ten olazapine-induced NMS cases reported (David and Remy, 1998). Like clozapine-induced NMS, major features of olanzapine-induced NMS were high fever, altered consciousness level, diaphoresis, elevated CPD, AST, and LDH level (David and Remy, 1998). Olanzapine-induced NMS without rigidity has also been reported (David and Remy, 1998). It has been argued that NMS associated with atypical neuroleptics such as clozapine or olanzapine may have a lower incidence of extrapyramidal effects because of selective dopamine blockade, with relative sparing of nigrostriatal pathways (Nopoulos *et al.*, 1990). Quetiapine is an atypical antipsychotic, and is a dibenzothiazepine derivative with greater *in vitro* binding affinity for serotonin 5-HT2A receptors than for dopamine D2 receptors (Saller and Salama, 1993; Casey, 1996). To our knowledge, several individual cases of quetiapine-induced NMS have been reported to date (Donna *et al.*, 2000). The incidence of NMS associated with antipsychotic use is approximately 0.5% (Gratz and Simpson, 1994). However, in clinical trials with quetiapine, the incidence of possible NMS was considerably lower (0.9%)

(Vikram and Jober, 2000). Like our case, only one NMS case was reported to be associated with three different atypical antipsychotics in an adult continuously (Bottlender *et al.*, 2002). Two cases were reported to be associated with two different atypical antipsychotics (Aboraya *et al.*, 2002; Gram, 2002). In terms of age, most of the NMS cases related with atypical antipsychotics were adults. One adolescent's case was reported to date (Robb *et al.*, 2002). However, there has not been a child case. Also, there is little literature about ethnic difference, including Asians, in NMS cases. This is the first NMS case that occurred in association with childhood administration of the three different atypical antipsychotics. This case suggests that the main symptoms of atypical antipsychotics-induced NMS in childhood are high fever and diaphoresis without rigidity. In laboratory findings, levels of CPK, CPK-MB, GOT/GPT and LDH are elevated. Also, the loss of consciousness hasn't occurred due to atypical antipsychotics-induced NMS, except risperidone. It is thought that EPS symptoms and the loss of consciousness are not included as common characteristics of NMS with atypical antipsychotics especially olanzapine and quetiapine. We could suggest three possibilities about these NMS characteristics. First, the period atypical antipsychotics were used would have been too short, except for risperidone. Second, pharmacological actions of atypical antipsychotics are different from those of typical antipsychotics, with a relatively high affinity for 5-HT receptors. Third, three different atypical antipsychotics-induced NMS cases could be attenuated by risperidone.

References

Aboraya A, Schumacher J, Abdalla E, Lepage J, McGhee M, Butcher D, Griffin H, Shahda M (2002) Neuroleptic malignant syndrome associated with risperidone and olanzapine in first-episode schizophrenia. W V Med J *98*: 63–65

Addonizio G, Susman V L (1987) ECT as a treatment alternative for patients with symptoms of neuroleptic malignant syndrome. J Clin Psychiatry *48*: 102–105

Bajjoka I, Patel T, O'Sullivan T (1997) Risperidone-induced neuroleptic malignant syndrome: a case report. Ann Emerg Med *30*(5): 698–700

Beasley Jr, C M Tollfson G D, Tran P D (1997) Efficacy of olanzapine: an overview of pivotal trials. J Clin Psychiatry *58* (Suppl. 10): 7–12

Bottlender R, Jager M, Hofschuster E, Dobmeier P, Moller H J (2002) Three episodes in one patient. Pharmacopsychiatry *35*: 119–121

Bymaster F D, Colligaro D O, Flacone J F (1996) Radio receptor binding profile of the atypical antipsychotic olazapine. Neuropsychopharmacology *14*: 87–96

Caroff S N, Mann S C (1988) Neuroleptic malignant syndrome. Psychopharmacol Bull *24*: 24–29

Caroff S N, Mann S C (1993) Neuroleptic malignant syndrome. Psychiatr Ann *77*: 185–202

Casey D E (1996) Seroquel: preclinical and clinical findings of a new atypical antipsychotic. Exp Opin Invest Drugs *5*: 939–957

David M, Remy C (1998) Case report: possible neuroleptic malignant syndrome associated with olanzapine. J Clin Psychopharmacol *18*(6): 485–486

Donna W, Steven E S, Joseph P (2000) Nonextrapyramidal side effects of novel antipsychotics. Curr Opin Psychiatry *13*(1): 45–50

Filice G A, McDougall B C, Ercan-Fang N (1998) Neuroleptic malignant syndrome associated with olanzapine. Ann Pharmacother *32*: 158–1159

Gram L F (2002) Neuroleptic malignant syndrome in the treatment with the new, atypical antipsychotic agents, risperidone and olanzapine. Ugeskr Laeger *162*: 1914–1915

Gratz S S, Simpson G M (1994) Neuroleptic malignant syndrome. Diagnosis, epidemiology and treatment. CNS Drugs *2*: 429–439

Hasan S, Buckley P (1998) Novel antipsychotics and the neuroleptic malignant syndrome: a review and critique. Am J Psychiatry *155*: 1113–1116

Jibson M D, Tanson R (1998) New atypical antipsychotic medications. J Psychiat Res *32*: 215–222

Kara gianis J L, Phillips L C, Hogan K P, Le Drew K K (1999) Clozapine-associated neuroleptic malignant syndrome: two new cases and a review of the literature. Ann Pharmacother *33*: 623–630

Kellam A M P (1987) The neuroleptic malignant syndrome, so-called: a survey of the world literature. Br J Psychiatry *150*: 752–759

Keyser D L, Rodnitzky R L (1991) Neuroleptic malignant syndrome in Parkinson's disease after withdrawal or duration of dopaminergic therapy. Arch Intern Med *14*: 794–796

Knezevic W, Mastaglia F, Lefroy R (1984) Neuroleptic malignant syndrome. Med J Aust *140*: 28–30

Latz S, McCracken J (1992) Neuroleptic malignant syndrome in children and adolescents: two case reports and a warning. J Child Adolesc Psychopharmacol *2*: 123–129

Mills K C (1993) Serotonin toxicity: a comprehensive review of emergency medicine. Top Emerg Med *15*: 54–73

Nopoulos D, Flaum M, Miller D D (1990) Atypical neuroleptic malignant syndrome with an atypical neuroleptic: clozapine induced neuroleptic malignant syndrome without rigidity. Ann Clin Psychiatr *2*: 2251–2253

Pearlman C A (1986) Neuroleptic malignant syndrome. J Clin Psychopharmacol *6*: 257–273

Robb A S, Chang W, Lee H K, Cook M S (2002) Risperidone-induced neuroleptic malignant syndrome in an adolescent [Case study]. J Child Adolesc Psychopharmacol *10*: 327–330

Saller C F, Salama A I (1993) Seroquel: biochemical profile of a potential atypical antipsychotic. Psychopharmacology *112*: 285–292

Shalev A, Muniz H (1986) The neuroleptic malignant syndrome: agent and last interaction. Acta Psychiatry Scand *73*: 337–347

Stanley A K, Hunter J (2000) Possible neuroleptic malignant syndrome with quetiapine. Br J Psychiatry *176*: 497

Steingard R, Khan A, Gonzalez A, Herzog D (1992) Neuroleptic malignant syndrome: review of experience with children and adolescents. J Child Adolesc Psychopharmacol *2*: 183–198

Stewart F (2002) Pharmacology of atypical antipsychotics. Clin Neuropharmacol *25*(3): 153–157

Tarshy D, Baldessarini R J, Tarazi F T (2002) Effects of newer antipsychotics on extrapyramidal function. CNS Drugs *16*: 23–45

Tsai G, Crisostomo G, Rosenblatt M L, Stern T A (1995) Neuroleptic malignant syndrome associated with clozapine treatment. Ann Clin Psychiatry *7*: 91–95

Vikram D, Jober R (2000) Quetiapine: a review of its safety in the management of schizophrenia. Drug Safety *23*: 295–307

Webster P, Wijeratne C (1994) Risperidone-induced neuroleptic malignant syndrome [letter]. Lancet *344*: 1228–1229