The Life Threatening Adverse Effects of Psychotropic Drugs: A Case Report

Ahmet Tiryaki, Gökhan Kandemir, İsmail Ak

SUMMARY

Neuroleptic malignant syndrome (NMS) is a rare idiosyncratic reaction to antipsychotic drugs that is potentially fatal. Characteristic features of NMS are hyperthermia, muscular rigidity, severe autonomic dysregulation and disturbed consciousness. Signs and symptoms of serotonin syndrome (SS) can be grouped into four inclusive categories that are almost identical to those of NMS. Clinically, NMS and SS share many features, suggesting different spectrums of a similar disorder. To make a distinction between the two is often difficult because of a large clinical overlap. We present a case of a 42-year-old male with a history of schizophrenia that developed signs and symptoms inconsistent with either NMS or SS after intramuscular administration of 2 typical antipsychotics along with 1 dose of a selective serotonin reuptake inhibitor (SSRI). The patient abruptly developed the clinical features in just 24 h. The patient presented with altered mental status and increased levels of creatinine phosphokinase. Twelve days of intensive care unit treatment was chiefly supportive and included bromocriptine. The final outcome was positive with complete disappearance of the symptoms. The treatment for both NMS and SS is similar. The therapeutic interventions primarily consist of removing the suspected agent and providing supportive care. We present this case to highlight some controversial issues concerning the life threatening adverse effects of psychotropic drugs, which illustrate the spectrum concept.

Key Words: Neuroleptic Malignant Syndrome, Serotonin Syndrome, symptoms, differential diagnosis

INTRODUCTION

Psychotropic drugs occupy an important place in current clinical practice. Although drugs are accepted as the first-line treatment approach in psychological disorders, they are in a significant position due to their severe, sometimes fatal side effects. Neuroleptic malignant syndrome (NMS) and serotonin syndrome (SS) are side effects that sometimes can only be diagnosed after the death of a patient. The relationship between NMS and SS has been discussed in terms of common physiopathological mechanisms and clinical characteristics (Wren et al., 2003; Kontaxakis et al., 2000). NMS is a rare, fatal side effect of antipsychotic treatment. It is still debatable as to what extent this side effect can occur with the use of new antipsychotic agents. NMS was first observed in clinical studies with haloperidol in 1960 (Reeves et al., 2002). The frequency of this syndrome in patients who receive antipsychotic treatment is 0.07%-2.2%, while the mortality rate is 10%-30%. NMS occurs due to the interaction between a sensitive individual and antipsychotic treatment. Two theories are suggested in the explanation of the syndrome; one considers central dopamine receptor blockade, the other, disorder of skeletal muscles (Chandran et al., 2003). Hyperthermia, muscular rigidity, prominent irregularity in autonomic functions, and changes in consciousness are the 4 main symptoms related to NMS. Its clinical presentation may vary depending on various factors. For example, severe intestinal hemorrhage accompanied NMS symptoms in a case with chronic renal failure (Hayashi et al., 2002). Sporadic cases associated with atypi-
cal antipsychotic drugs, particularly with the ones that cause powerful dopamine blockage, have also been reported (Stanfield and Privette, 2000). Some 96% of the cases arise within the first 30 days following antipsychotic administration and improve 5-10 days after the cessation of the drug, with supportive treatment (Liebold et al., 2004; Kontaxakis et al., 2002; Stanfield and Privette, 2000). Serotonin plays a key role in the treatment of depressive mood disorders. Selective serotonin reuptake inhibitors (SSRIs) increase serotonin levels. This group of drugs is in widespread use because they are safer than the antidepressants that preceded their development. However, serotonin increase may cause side effects. The most severe side effect is SS, which can cause death. This syndrome can be observed with drugs that increase serotonin release, inhibit serotonin reuptake, or change the response to serotonin. SS occurs due to over-stimulation of 5-HT1A receptors. It was first reported in 1960 (Keck and Arnold, 2000). The frequency of the syndrome’s occurrence is unknown. Many cases with early mild symptoms have not been recognized and thus have not been reported. More severe cases have been misinterpreted as NMS and have been falsely and incompletely reported (Bertolín-Guillèn et al., 2004). Symptoms and signs in critical functioning, including the central nervous and neuromuscular systems, as well as autonomic irregularity, have been defined; however, there may also exist clinical presentations, which do not yield symptoms and signs in all systems. SS develops quickly, within 24 h after excessive intake of serotonergic agents or their combined usage and has no predominance based on gender or age (Bryant, 2004). Clinical manifestations related to the syndrome have been classified as mild symptoms associated with serotonin, serotonin syndrome and toxic state (coma, generalized tonic-clonic seizures, and body temperature = 40°C) (Birmes et al., 2003). SS may present with autonomic symptoms, such as confusion, agitation, anxiety, myoclonus, increased deep tendon reflexes, tremor, diarrhea, hypertension, tachycardia, and fever, in addition to some other symptoms, such as coordination disorder in motor functions. A supportive approach is essential in the treatment. There are case reports in which total recovery was achieved primarily with benzodiazepines, and propranolol, chlorpromazine, and nitroglycerine in prolonged cases. Today, there is no well-defined treatment for SS (Brown, 2004; Rivera et al., 2003). The aim of this report was to discuss the common and different aspects of NMS and SS, with regard to physiopathological and clinical features, by reporting a case that consulted to the emergency room.

Case report

One day before presenting to the hospital, a 42-year-old male patient with the diagnosis of chronic schizophrenia for 10 years, had an injection of flupenthixol and zuclopenthixol depot, which he had been using for the previous 3-4 months. Considering the depressive symptoms, citalopram 20mg/day was also commenced. The patient was brought to the emergency room after he was found unconscious at home. In his neurological examination he was unconscious, light reflex was positive on both sides, pupils were isochoric, oculocephalic reflexes were positive, stiff neck and lateralization in motor examination were absent, deep tendon reflexes were active, and Babinski reflex was absent on the right side. No additional pathological finding was observed in the examination. Complete blood count and biochemical tests showed no abnormality, except a high leukocyte count (22.500/mm³). Both the psychiatric and neurological consultations recommended computed tomography, which was normal. Creatinine kinase, creatinine kinase-MB, and myoglobin values were well above the normal range [2813 U/L (0-170), 95 U/L (0-24), and 3000 ng/ml (0-70), respectively]. Cardiology consultation revealed no cardiac problem. The patient was monitored for 24 h in the emergency room. The treatment was continued in the intensive care unit due to the patient’s unchanged consciousness state, increasing and unstable blood pressure, fever (39.6°C, lowered by peripheral cooling), and deteriorated general condition. The patient was followed-up with supportive and bromocriptine treatment. Within the first 4 days, unconsciousness, autonomic irregularity, increase in muscle destruction products, and leukocytosis were consistent with NMS and SS; however, high fever was not observed. During the follow-up, regarding the clinical examination and laboratory findings, no prominent evaluation could be made in favor of either of the 2 syndromes. Within the following days, the patient had fever once (39°C), and this was considered to be due to Klebsiella infection related to the central catheter. On the 6th day the patient began to breathe spontaneously. On the 8th day he regained consciousness. On the 9th day his orientation and cooperation were complete.
and oral feeding began. On the 11th day his urinary sounder and arterial catheter were removed, and he was discharged on the 12th day, with normal clinical and laboratory findings. Bromocriptine treatment was continued for 3 months. One month after the injection of depot form antipsychotics, he was diagnosed as resistant schizophrenia, paranoid subtype, and clozapine treatment was begun.

**DISCUSSION**

The suggestion that SS is a milder clinical condition than NMS has not been accepted by some authors. Both are considered severe conditions, which can lead to death (Wren et al., 2003). Delirium, fever, muscular destruction, dilated pupils, tachycardia, excessive sweating, rigidity, and instability in blood pressure may be observed in both syndromes. The differentiation of these 2 similar syndromes can be made by the overall appearance of the patient. In SS, the patient is restless and active, and there is myoclonus and incoherent speech. Catatonic symptoms like immobility, quietness, and starring at a certain point are dominant in NMS. Although muscular destruction is seen in both syndromes, disseminated intravascular coagulation (DIC), seizures, ventricular tachycardia, and severe hypotension are quite rare in NMS (Garside and Rosebush, 2003). There are many common properties, which point out that a clinically similar disorder has different expressions. Increased body temperature, cognitive changes, leukocytosis, increased creatine kinase levels, neuromuscular changes, increase in transaminase levels, and decreased bicarbonate levels can be observed in both syndromes. Because of multiple drug usage in psychiatric treatment and multiple neurotransmitter effects of drugs, it is rather difficult to make a diagnostic distinction between these 2 clinical conditions. On the other hand, when the effect mechanisms of new antipsychotics are considered, the possible side effects are remarkable in this regard. SS and atypical NMS cases have been reported in association with atypical antipsychotic drugs (Duggal and Fletchko, 2002; Atbaşoğlu et al., 2004). The most commonly accepted mechanism involved in the onset of SS is the over excitation of serotonin receptor subtype 1A (5-HT1A). Drugs like risperidon and ondansetron, which are the antagonists of other serotonin subtypes (5-HT2 and 5-HT3), have also been reported to cause this syndrome. Moreover, it is thought that inhibition of the production and release of presynaptic dopamine plays a role in the onset of SS and NMS (Avarello and Cottone, 2002). In the differential evaluation, it is important to note that NMS has higher body temperature and prominent extrapyramidal symptoms, while SS has lower body temperature, myoclonus, and gastrointestinal irregularity. Another point to consider is that the duration of antipsychotic drug usage is longer in cases of NMS, whereas only 1 dose can be enough to trigger the onset of SS (Table 1). In the present case, neither the above-mentioned clinical characteristics nor the duration of drug use could be associated with any of the 2 syndromes. The ambiguity in the clinical appearance can be explained by the use of high-dose typical antipsychotic drugs for a while and simultaneous SSRI usage. In the absence of diagnostic certainty, agents such as cyproheptadine, chlorpromazine, methysergide, which are suggested for the treatment for SS were not given to this patient. Increased levels of muscular destruction products were considered to be a serious

<table>
<thead>
<tr>
<th>Drug history</th>
<th>NMS</th>
<th>SS</th>
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<tr>
<td>Onset duration</td>
<td>Usually an antipsychotic</td>
<td>Serotonin enhancer</td>
</tr>
<tr>
<td>Physiopathology</td>
<td>Hypodopaminergic state</td>
<td>Hyperserotonergic state</td>
</tr>
<tr>
<td>Increased body tempeature</td>
<td>With a frequency of 90%</td>
<td>With a frequency of 46%</td>
</tr>
<tr>
<td>Muscle tone myoclonus</td>
<td>R rigidity, rhabdomyolysis</td>
<td>Increased reflexes, restless,</td>
</tr>
<tr>
<td>Mortality rate</td>
<td>Higher than SS</td>
<td>Lower than NMS</td>
</tr>
<tr>
<td>Autonomic symptoms</td>
<td>More than SS</td>
<td>Less than NMS</td>
</tr>
<tr>
<td>Recovery duration</td>
<td>Ave. 5-10 days</td>
<td>Ave. &lt;24 hours</td>
</tr>
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risk factor for renal failure, although no muscular rigidity was detected. At this point in time, for the treatment of these 2 syndromes, the advantage for patient and clinician alike is that cessation of the drug suspected of triggering symptoms and supportive treatment can be sufficient. Supportive treatment including antipyretic drugs such as aspirin and acetaminophen, environmental cooling, intravascular liquid support, myorelaxant agents, and mechanical ventilation, when necessary, has been regarded as the major approach. Although no accepted and unchangeable approach was suggested for the treatment, dantrolene and bromocriptine may present a common way. Educating patients, family members, and caregivers about these side effects increases the chance of early diagnosis, immediate intervention and reduces the risk of mortality. The fatal side effects of psychotropic agents are often associated with the use of multiple drugs with similar effect mechanisms, rapid increase in dose, and high drug doses. Doctors need to be aware of these probable risk factors when prescribing antipsychotic treatment. As new drugs with different effect mechanisms and suggestions about the combined use of drugs increase, the features of the side effects vary and increase. To clarify whether SS and NMS are the different aspects of a common physiological process determined by different intermediary variables requires further elucidation through additional novel studies.

REFERENCES