STRUČNI ČLANCI
PROFESSIONAL ARTICLES

Clinical Centre of Vojvodina, Novi Sad
Clinic for Psychiatry

Stručni članak
Professional article
UDK 615.214.06:616.89
DOI: 10.2298/MPNS1010705C

SIDE EFFECTS OF ANTIPSYCHOTIC AGENTS – NEUROLEPTIC MALIGNANT SYNDROME

NEŽELJENI EFEKTI PRIMENE ANTIPSIHOTIKA – NEUROLEPTIČNI MALIGNI SINDROM

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Summary – Neuroleptic malignant syndrome is a rare, potentially life-threatening complication which is an unpredictable, idiosyncratic reaction to antipsychotics. In patients receiving traditional antipsychotics, neuroleptic malignant syndrome occurs with an incidence of 0.2–3.3%. However, neuroleptic malignant syndrome also appears in patients treated with atypical antipsychotics, especially Clozapine. A possible cause of neuroleptic malignant syndrome is blockade of dopamine receptors in the nigrostriatal tracts or hypothalamic nuclei. If signs and symptoms of the Neuroleptic malignant syndrome are identified in time, full recovery is possible. This is a report of a female patient with neuroleptic malignant syndrome treated by traditional antipsychotics. As soon as neuroleptic malignant syndrome symptoms were recognized, the antipsychotic drugs were discontinued, symptomatic therapy was initiated and symptoms of neuroleptic malignant syndrome disappeared. However, the patient's psychotic symptoms persisted and an atypical antipsychotic was administered. During the next few days the psychotic symptoms gradually disappeared and the patient accomplished good recovery.

Key words: Antypsychotic Agents + adverse effects; Neuroleptic Malignant Syndrome; Signs and Symptoms

Introduction

Neuroleptic malignant syndrome (NMS) is a rare, idiosyncratic, potentially life-threatening complication reported to occur during therapy with both traditional and atypical antipsychotic agents [1,2]. After neuroleptics were introduced for clinical use in 1952 [3], Delay described clinical features of the malignant neuroleptic syndrome for the first time: development of pronounced extrapyramidal symptoms (hyperthermia, „cogwheel rigidity", tremor, dystonia); hyperthermia (up to 42 degrees C), altered mental status of quantitative (somnolence, spoor, coma) or qualitative type (confusion-delusion clinical picture). NMS also includes a dysfunction of the autonomic nervous system (unstable hypertension, orthostatic hypotension, tachycardia - over 80/min, diaphoresis, hypoxia, incontinence, and sialorrhea). Symptoms of NMS are also associated with abnormalities in laboratory findings such as: leukocytosis (10 – 40.000 with a shift to the left, which is optional) (4 – 6), increase in creatinine-phosphokinase (CPK) due to rhabdomyolysis (reference values: 24 – 170 j/l), electrolytic imbalance associated with hypokalemia, acidosis and increase in transaminases [1,2,4,5].

Over the years, along with the frequent use of psycho-pharmaceuticals of varied actions, articles describing development of NMS as a rare, life-threatening complication associated with adverse effects of antipsychotics, became more frequent as well [2,6,7].

According to current medical literature, the incidence of NMS in different parts of the world is similar (ranges from 0.2 – 3.3% of patients treated with antipsychotic agents), and there are no significant differences in regard to application of traditional and atypical antipsychotics [4,6-8]. It is important and significant to point to the fact that the number of lethal outcomes among patients with NMS has significantly decreased, from 25% prior to 1984, to 7-11% [7] over the last years. It is considered that timely detection of initial symptoms and immediate actions are the reasons for reducing the percentage of lethality in NMS patients.

That is why it is of utmost importance to detect initial symptoms and start adequate therapeutic procedures [1–7]. Although there are no significant differences in the incidence of NMS during the use of traditional (TA) and atypical antipsychotics (AA), it has been established that extrapyramidal symptoms are less common in the clinical picture of patients with NMS receiving AA, which is explained by different actions (lower affinity to D_2 receptors in the nn. striate and substantia nigra).

In the literature [2,3] physicians may find factors which may warn them of an increased risk of NMS development. They include the following: rapid increase in the dosage of antipsychotics, dehydration, psychomotor agitation, i.m. application of antipsychotics, organic brain damage (IVC, Parkinson and Wilson's disease, addicts), fixation over a longer period of time, male gender, younger age (under the age of 50 years), concomitant administration of an-

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tipsychotics (Topical calcineurin inhibitor (TCI), lithium salts, other antipsychotics), abrupt discontinuation of anticholinergic medications.

NMS usually appears after 2 – 15 sessions of antipsychotic therapy, but this idiosyncratic reaction to neuroleptic drugs may also develop after a longer administration of the same drug [6–8].

Symptoms usually follow one another, whereas muscular hypertonia and altered mental status are among the first (hyperthermia, diaphoresis and so on). That is why timely detection and identification of extrapyramidal symptoms is of greatest importance, as well as rapid correction of therapy.

Clinically manifested NMS gradually disappears after 5 – 14 days after discontinuation of neuroleptic therapy, but in cases where depot preparations were used, the symptoms may persist up to a month.

The physiopathological mechanism of NMS is explained by the iatrogenic blockade of dopamine receptors (D_2) of the nigrostriatal, mesocortex and hypothalamic nuclei. This theory has been widely accepted, but it has been relativized by introduction of atypical antipsychotic agents into clinical practice [7,8]. Atypical antipsychotics show significantly lower affinity to D_2 receptors, but this fact does not explain why NMS appears when they are applied. Therefore it is considered that the dysfunction between dopamine-ergene, GABA-ergene and acethylcholine transmission in the CNS, plays the main role in the development of NMS, whereas until recently it has been believed that it was caused only by blockade of D_2 receptors [5–9].

A current assumption is that apart from the development of this idiosyncratic reaction to antipsychotic agents, the genetic predisposition also plays a role [8–10], while genetic investigations point to allelic polymorphism of dopamine receptors in patients with NMS [9].

However, up to the present, numerous theories have failed to answer why only in a small number of patients treated with antipsychotic drugs NMS develops in the first place. It is still assumed that the interaction of several factors causes these adverse effects of psycho-pharmacotherapy [10,11].

Differential diagnosis includes the following:

1) Malignant hyperthermia, in which there are data on application of inhalation anesthetics and succinylcholine (specific therapy of dantrolene 10 mg/kg/bw, or 50 – 600 mg/day.
2) Lethal catatonia – in which there are heteroanamnestic data about extreme psychotic alterations and psychomotor excitement before catatonia (electroconvulsive therapy (ECT) is recommended);
3) Pronounced extrapyramidal symptoms (absence of hyperpyrexia, leukocytosis, laboratory findings);
4) CNS infections (meningitis, encephalitis). The diagnosis is based on CT, lumbar puncture (LP), and MRI findings;
5) Intoxications – data on receiving various toxic matters, toxicological tests.

According to the recommendations of the WHO, patients with NMS are treated in intensive care units. The first intervention includes discontinuation of antipsychotics as well as of other psycho-pharmaceuticals (lithium salts, other antipsychotics).

A dopamine antagonist – bromocrintine (2.5 – 40 mg/day) is recommended, and a possible application of dantrolene in hyperpyrexia (myorelaxant), as well as fluid replacement, symptomatic therapy, acidosis and hypokalemia correction, combined with treatment of complications due to rhabdomyolysis; decubitus often develops within 24 hours [8–10].

Broad-spectrum antibiotics are recommended, heparin in prevention of disseminated intravascular coagulation (DIC) and pulmonary embolism, as well as benzodiazepine, and if necessary, ECT.

After the withdrawal of all NMS symptoms, antipsychotic agents are discontinued from 5-14 days in order to decrease the risk of new development of NMS.

During the wash-out period, the following agents are used: clonazepam, lorazepam, mood elevators, if necessary, antipsychotic agents of different mechanisms of action (clozapine, olanzapine) with low affinity for dopamine receptors [7,10]. Depot preparations are excluded from the therapy.

Some complications of NMS

Extreme rhabdomyolysis may be associated with renal insufficiency, deep vein thrombosis, and pulmonary embolism. Complications are mostly due to consciousness disorders, immobilization, impaired swallowing reflex, dysphagia, aspiration pneumonia, dehydration, heart arrest [3,5,7,9].

Due to a serious clinical picture and appearance of life-threatening NMS, it is necessary to inform members of the patient's family about the course of the disorder and keep detailed medical records.

Case report

This is a report of a 46-year-old woman born in Novi Sad. She is divorced and lives alone. She has secondary education, but has lost her job and only occasionally visits her parents who live in the same place. According to the auto-anamnestic evidence, during puberty and adolescence she sometimes used to abuse alcohol and marijuana. Her first admittance to the Institute of Psychiatry in Novi Sad was in 2002, and she was treated in a Daily Hospital Unit of the Clinic for Affective and Anxiety Disorders. She was discharged with the (F 43.2) diagnosis of prolonged depressive reaction and (F 60.3) borderline personality disorder, according to the ICD-10 Classification of Mental and Behavior Disorders. She was admitted to the Daily Hospital after a series of conflicts in her family. She often fought with her husband and started drinking heavily. Her outpatient treatment lasted for three months, but as there was no improvement, she was admitted for partial hospitalization. She com-

plained of apathy, no perspective, irritability, appetite and sleep disorders, ineffectiveness and crying spells. The therapy included mood elevators, antidepressants and low doses of antipsychotics. Combined with psychotherapy, this treatment led to an improvement and four months later she was discharged from hospital, showing satisfactory social remission. The outpatient therapy continued.

After discharge, the patient soon stopped taking medications on her own initiative, occasionally had control check-ups and managed to function at home and at work.

The following hospitalization occurred in the period of October – December, 2008. She was taken to hospital by ambulance accompanied by her mother, after the police intervention. According to information received from the mother, her daughter's behavior changed about 10 days before the admittance. She became outspoken, suspicious and exhibited poor communication. The clinical picture differed from that on the previous admittance. The patient was confused, upset, with dissociative thoughts, numerous delusions with paranoid interpretation, xenopathic experiences and auditory hallucinations.

The patient received the following therapy: haloperidol injections 3 x 1 i.m., bensedine 3 x 1 i.m. The same therapy was continued the following day. After the therapy the patient was calmer, cooperative, but some psychopathologic behavior persisted, so she started receiving her therapy per os. Due to shortage of 2 mg haloperidol tablets, rispolept was initiated, but the dosage of antipsychotics was increased to 3 mg per day, and benzodiazepine injections were continued.

On the fifth day of her hospital stay, the patient developed extrapyramidal symptoms including hypertonia (cog-wheel rigidity), associated with severe generalized extrapyramidal tremor, hyperhydrosis and ''facies oleosa''. Her state of consciousness varied from somnolence to confusion (psychotic clinical picture). During the same day the patient presented with hyperthermia (37.7 – 38.2 degrees C), labile hypertension (up to 160/100); profuse sweating, tachycardia (up to 120/min), and regular heart rate rhythm.

The laboratory findings revealed increased CPK levels (1540 j/l), hypokalemia (k – 3.3 mmol/l), and increased leukocytosis (3.6 on admission, 6.76 with a tendency to „turn to the left").

The antipsychotic agent was completely discontinued and bromkriptin was introduced (5 mg/day), as well as infusion solutions, potassium replacement in the infusion, and a urinary catheter was placed (diuresis was over 1500 mg/day). According to the internist's recommendations, a wide-spectrum antibiotic was added to the infusion. Antipyretic paracetamol was also initiated (3x1), antihypertensive presolol (100 mg 3x1/4) and monopril (20 mg, 2x1). Lorazepam tablets (7.5 mg/day) were given for sedation.

During the next few days the patient was refreshed, fully conscious, but still severely psychotic and subfebrile. The laboratory findings were within reference values, extrapyramidal symptoms regressed.

Due to the psychotic clinical picture with paranoid interpretation and risk of repeated agitation, clozapine, an atypical antipsychotic (12.2 mg/day) combined with clonazepam (2.5 mg/day) were initiated.

During the following 10 days, the dosage of antipsychotics was increased to 200 mg/day. The patient reacted positively and psychopathologic symptoms disappeared. She was allowed to spend therapy weekends at home, and they seemed to be more and more successful.

The patient was discharged from hospital at the level of social remission with the recommended outpatient treatment.

Our patient presented with symptoms induced by adverse effects of the antipsychotic therapy - that is NMS, with an only exception of severe leukocytosis. Taking into account that her initial values of leukocytes were low, it may be supposed that timely therapeutic procedures caused only moderate increase of leukocytes, that is that the clinical picture of NMS was not completely developed.

Discussion

According to the literature data (1, 3), 79% of patients with NMS make a complete recovery, whereas possible consequences include cognitive disorders, neurological focal deficits, muscle atrophy and contractures.

Since NMS is a very serious complication which commonly occurs during application of antipsychotics and which still has an unpredictable outcome, it is of utmost importance to follow up all side-effects of antipsychotic therapy, such as extrapyramidal symptoms. A timely intervention can prevent development of the complete clinical picture of NMS, and at the same time decrease possible secondary infections and complications of NMS [1,7,9].

Conclusion

The presented case of neuroleptic malignant syndrome was most probably induced by administration of an antipsychotic – haloperidol, but possibly by its combination with rispolept. This means that these antipsychotic agents may not be used in this patient due to an extremely high risk from neuroleptic malignant syndrome development. Instead, an atypical antipsychotic was used (clozapine), with different mechanisms of action, and a satisfactory therapeutic effect was achieved – a significant reduction of psychotic symptoms. An outpatient treatment using the same therapy was recommended.

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Sažetak

Uvod

Neuroleptički maligni sindrom je retka, ali po život opasna komplikacija koja nastaje usled neželjenih dejstava antipsihotičkih lekova. U savremenoj literaturi navodi se inidencija od 0,2 do 3,3%. Neuroleptički maligni sindrom često nastaje posle naglog povećanja doze konvencionalnih neuroleptika ili u stanju dehidriranosti. Međutim, ovaj sindrom može da se javi i kod bolesnika lečenih atipičnim antipsihoticima, češće kod primene Clozapina. Patofiziološki mehanizam nastanka neuroleptičkog malignog sindroma objašnjava se jatrogenom blokadom Dopaminskih receptora (D2) nigrostriatuma, mezokorteksa i hipotalamičkih jedara. Ukoliko se najznačajniji simptomi ovog sindroma (mišićna hipotonija, promene svesti, hipertermija, dijaforeza i sl.) pravovremeno uoče i na njih se promptno reaguje, moguć je potpuni oporavak.

Prikaz slučaja

Ovo je prikaz slučaja bolesnice lečene konvencionalnim antipsihoticima. Pošto su simptomi neuroleptičkog malignog sindroma blagovremeno uočeni, antipsihotička terapija je odmah prekinuta, uvedena je simptomatska terapija, a njegovi simptomi su nestali. Međutim, s obzirom da su psihotički simptomi i dalje bili prisutni, uvedena je terapija atipičnim antipsihoticima. Tokom sledećih nekoliko dana, psihotički simptomi su se povukli i ustanovljen je dobar oporavak bolesnice.

Diskusija i zaključak

Budući da je neuroleptički maligni sindrom komplikacija potencijalno opasna po život, koja nastaje usled neželjenih dejstava neuroleptičkih lekova, neophodno ih je uočiti kod svakog bolesnika, a ukoliko se pojave simptomi neuroleptičkog malignog sindroma, potrebno je odmah prekinuti terapiju antipsihoticima. Ako je neophodno izvršiti zamenu leka, potrebno je da lek ima nizak afinitet prema (D2) receptorima, i da se kombinuje sa simptomatskom terapijom.

Ključne reči: *Antipsihotici + neželjeni efekti; Neuroleptični maligni sindrom; Znaci i simptomi*

Rad je primljen 7. VIII 2009.
Prihvaćen za štampu 5. X 2009.
BIBLID.0025-8105:(2010):LXIII:9-10:705-708.