Cardiac Arrest Due to Neuroleptic Malignant Syndrome A Case with Acute Antipsychotic Drug Overdose: Case Report

AŞIRI DOZ ANTİPSİKOTİK İLAÇ ALIMINA BAĞLI GELİŞEN NÖROLEPTİK MALİGN SENDROM SONUCU KARDİYAK ARREST

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Abstract

We present a case diagnosed with neuroleptic malignant syndrome (NMS) as a result of moclobemid and thioridazine overdose. The 42-year old patient was admitted to the intensive care unit was administered symptomathic treatment and replacement therapy with dantrolene-Na. The patient developed a sudden cardiac arrest. Sinus rhythm was obtained after cardiopulmonary resuscitation. His mental and respiratory status improved gradually and he was extubated after a short weaning period at day 5. Full dose antipsychotic medication was initiated. He was discharged at day 7. We aimed to discuss the treatment strategies of NMS; management of fluid and electrolyte abnormalities, ventilatory support, dantrolene-Na and symptomatic treatment.

Key Words: Neuroleptic malignant syndrome, intensive care units, moclobemide, thioridazine

Özet

Nöroleptik malign sendrom (NMS); antipsikotik ajanlarla tedavide gelişen ölüm potansiyeli bulunan bir komplikasyondur. Kronik psikoz öyküsü olan 42 yaşındaki erkek hasta, aşırı dozda moklobemid ve tioridazinin almasından ötürü acil servise başvurmuş. Hastaya NMS tanısı konularak semptomatik ve replasman tedavisi ile Dantrolen-Na başlandı. Hastada ani bir kardiyak arrest gelişmesi üzerine kardiyopulmoner resüsitasyon başlandı. On beş dakika süren CPR sonucu hasta sinüs ritmine döndü, nabzı alınmaya başlandı. Hastanın bilinç ve solunumunun giderek düzelmesi üzerine kısa bir süre weaning uygulanarak 5. günde ekstübe edildi. Aşırı doz antipsikotik alan hastalarda çok ciddi klinik tablosu olan NMS gelişip bazen de kardiyak arrest ile sonuçlanabileceği için, hastaların YBÜ'de izlenmesi gerektiği kanısındayız.

Anahtar Kelimeler: Nöroleptik malign sendrom, dantrolen-Na, yoğun bakım ünitesi

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NMS is a potentially lethal complication of treatment with antipsychotic drugs. NMS presents as a syndrome of extrapyramidal and autonomic dysfunction and is characterized by rigidity, tremor, hyperpyrexia, bradykinesis, tachycardia, labile blood pressure and altered consciousness.[1-6]

We present a case with cardiac arrest as a result of moclobemid, a monoamine oxidase inhibitor, and thioridazine, a neuroleptic drug overdose. We believe that patients with antipsychotic drug overdose who may present with cardiac arrest should be treated in the Intensive Care Unit (ICU). Our aim was to review the treatment modalities in the ICU in these circumstances.

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Case Report

A 42 year old man with a history of chronic psychosis was admitted to the emergency room with altered consciousness. He was in respiratory distress due to rigidity. His blood pressure was 110/90 mmHg, the heart rate was 120 beats/min and his breathing was 24 breaths/min. Arterial blood gas (ABG) analysis revealed a pO_2 of 68 mmHg, pCO_2 of 47 mmHg, pH of 7.51 and O_2

saturation of 83%. Thus, oxygen was applied at a rate of 4 L/min via a facemask.

Except for leukocytosis, laboratory studies such as complete blood count, biochemistry, chest x-ray and ECG were within normal ranges. The patient gave a history of taking 8 tablets of (2400 mg) moclobemide (Aurorix®) and 10 tablets of (1000 mg) thioridazine (Melleril®) 4 hours ago. His body temperature was approximately 40ºC, consequently blood and urinary cultures were obtained. Then he became unconscious and his respiratory distress worsened. In his second ABG blood gas analysis while he was taking 4 L/min O_2, pH was 7.16, and the other parameters were as follows: pO_2 53 mmHg, pCO_2 53 mmHg, SO_2 79.3%, HCO_3-16.8 mmol, Bex-8.1 mmol. Finally he had respiratory arrest and he was immediately intubated and admitted to the ICU. Mechanical ventilation was initiated. Laboratory analysis revealed hypocalcemia (8 mg/dL), leukocytosis (17000/cc), elevated serum creatinine phosphokinase (CPK) (30000 IU/L), elevated liver enzymes (AST: 873 IU/L, ALT: 168 IU/L) and elevated LDH (2019 IU/L), BUN 32 mg/dL, creatinine 1.1 mg/dL, and coagulation profile within normal ranges. Patient's daily ABG values, complete blood count, and biochemistry results are shown in Table 1. His rigidity, tremor and convulsions were treated with 5 mg diazepam IV. However, it failed to control his convulsions; thus, 250 mg of thiopenthal and 40 mg of atracurium were administered. After instituting dantrolene-Na at a loading dose of 40 mg, the maintanence dose was escalated to 1 mg/kg/24 hours. Unfortunately, the patient developed a sudden cardiac arrest. Cardiopulmonary resuscitation was started immediately and he was defibrillated twice for ventricular fibrillation. Sinus rhythm was obtained after a fifteen-minute cardiopulmonary resuscitation. Arterial blood pressure was normalized with inotropic drugs. Based on his history and dramatic clinical findings, the patient was diagnosed with NMS; symptomatic and replacement treatments were initiated. Hyperthermia was controlled with metamizol and cold application over the following two days. Dantrolene-Na was continued for three more days to treat his rigidity. In the mean time, his hemodynamic values and laboratory findings were within normal ranges. The following days his mental and respiratory status improved gradually and he was extubated after a short weaning period at day 5. Full dose antipsychotic medication was initiated. He was consulted to the psychiatry department for his

Table 1. Daily values for arterial blood gas (ABG), leukocyte and hepatic enzymes.

	Admission	**Postintubation**	**Deconnecting time**	**Preextubation**	**Postextubation**	**Recovery time**
	Mask with 4 L/min O2	Fi O2 % 40	T piece with 4 L/min O2	T piece with 4 L/min O2	Mask with 4 L/min O2	Air room
pH	7.16	7.25	7.50	7.44	7.45	7.43
pO2	53 mmHg	76 mmHg	109 mmHg	90 mmHg	110 mmHg	116 mmHg
pCO2	53 mmHg	38 mmHg	34 mmHg	36 mmHg	37 mmHg	35 mmHg
sO2 (%)	79	96.6	95.5	96.7	95.2	97.9
Na^+	126 mmol	130 mmol	132 mmol	134 mmol	138 mmol	140 mmol
K^+	4.5 mmol	5.1 mmol	3.7 mmol	3.9 mmol	3.7 mmol	4.0 mmol
Ca^+	8 mg/dL	8.2 mg/dL	8.6 mg/dL	8.8 mg/dL	9.1 mg/dL	9.4 mg/dL
Glucose	223 mg/dL	186 mg/dL	147 mg/dL	126 mg/dL	116 mg/dL	114 mg/dL
Lactate	47 mg/dL	21 mg/dL	14 mg/dL	10 mg/dL	8 mg/dL	2.2 mg/dL
$HCO3^-$	16.8 mmol	18.2 mmol	26.3 mmol	26.1 mmol	25.5 mmol	27.5 mol
Bex (BE)	-8.1 mmol	-6.1 mmol	2.1 mmol	1.9 mmol	1.1 mmol	3.5 mmol
Hb	14.6 g/dL	14.3 g/dL	14 g/dL	13.9 g/dL	14 g/dL	14.1 g/dL
Hct (%)	43.8	43.2	42	41.7	42	42.3
CPK	30000IU/L	24000 IU/L	16000 IU/L	7240 IU/L	3100 IU/L	850 IU/L
AST	873 IU/L	649 IU/L	482 IU/L	240 IU/L	124 IU/L	80 IU/L
ALT	168 IU/L	128 IU/L	88 IU/L	64 IU/L	48 IU/L	32 IU/L
LDH	2019 IU/L	1860 IU/L	1460 IU/L	840 IU/L	580 IU/L	366 IU/L
Leukocyt	17000/cc	13000/cc	11000/cc	8400/cc	6600/cc	5500/cc

chronic psychosis and alcoholism and was discharged at day 7.

Discussion

NMS is believed to be the result of central dopamine receptor blockade (DRD_2). In several studies, the pathophysiology of NMS was explained by a central hypodopaminergic state and a close association was found between DRD_2 blockade by neuroleptic drugs and the development of NMS.[2,4,5]

History of drug exposure helps to make the diagnosis. Several drugs such as phenothiazines, thioxanthenes or combinations of these drugs with each other or lithium, tricyclic antidepressants and metoclopramide were demonstrated to have similar potential.[2,4,6]

Typically, NMS tends to develop over hours to several days. In fulminant cases when hyperthermia exceeds 40ºC, the core pathology of the syndrome may be a direct cause of death. Such extreme temperature elevations may directly cause seizures, arrythmias, disseminated intravascular coagulation and cardiopulmonary failure.[4,7] As the body temperature of our case did not exceed 40ºC, we believed that with an intense and appropriate treatment he would be saved.

The syndrome may present with mild to severe forms and may resolve spontaneously with discontinuation of the stimulating drugs. In complicated cases, rhabdomyolysis and associated complications such as metabolic acidosis, myoglobinuria, renal and respiratory failure, shock, seizures and coma may be observed. Mortality rates are approximately 20%.[2,4,6]

The diagnosis of NMS may be difficult to make because many conditions mimic the syndrome. The differential diagnosis of NMS is extensive, including encephalitis, catatonia, heat stroke, toxic encephalopathy, hyperthyroidism, allergic reactions and metabolic problems such as hypocalcemia and hypomagnesemia.[3] Laboratory studies are not very helpful. Serum creatinine kinase is usually elevated. Leukocytosis is present in up to 79% of cases. Elevations of hepatic enzymes and electrolyte imbalances were reported.[4] Likewise, in our case we noted hypocalcemia (8 mg/dL), leukocytosis (17000/cc), elevated serum CPK (30000 IU/L), elevated liver enzymes (AST: 873 IU/L, ALT: 168 IU/L) and elevated LDH (2019 IU/L).

The diagnostic criteria of NMS are divided into major and minor findings. Among major findings are hyperthermia, rigidity, autonomic dysfunction, altered consciousness and elevated serum creatinine and phosphokinase values. Minor findings are tachycardia, labile blood pressure, tachypnea, akinesia, tremor, dystony, dysphagia, dyspnea, sialorrhea, incontinence, pallor, flushing and leukocytosis. Three major or two major and four minor findings are suggested to be diagnostic for NMS.[4] In our case the NMS diagnosis was based on three major findings-hyperthermia, rigidity and unconsciousness and three minor findings-tremor, dyspnea and tachycardia-as well as the history of antipsychotic drug treatment.

Treatment of NMS involves correcting fluid and electrolyte abnormalities and treating fever. If dystonia and rigidity are severe enough to physically limit respiration, intubation and ventilatory support may become necessary.[7] Our case was kept in the ICU intubated, in order to correct fluid and electrolyte abnormalities and support ventilation.

Over the past twenty years, several different medications have been tried. Among these drugs, bromocriptine and other dopaminergic agents, dantrolene-Na and benzodiazepines are of benefit.[7-10] Amantadine was successfully used to treat the syndrome. Bromocriptine and danrolene sodium are the most well established pharmacologic agents for treatment of moderate to severe NMS. Dantrolene seems to be the most effective drug in the presence of rigidity.[7,11]

Dantrolone-Na is the main agent for treatment of malignant hyperthermia. A direct acting skeletal muscle relaxant, dantrolene's mechanism of action is to block intracellular calcium efflux and thus interfere with excitation contraction coupling. It reduces heat production and contraction and exerts its effects within minutes of administration. Its

dose ranges from 1 to 10 mg/kg/day.[7,12] In several studies dantrolene was found to reduce mortality rate and time to symptom resolution.[11,12]

Sedative and muscle relaxant drugs were applied in our case. As stated in the literature, we tried to treat rigidity, our main problem, with dantrolene-Na alone and continued dantrolene sodium treatment for three days until rigidity was controlled.

Many authors believe that electroconvulsive treatment may take place as a second line intervention where pharmacological treatment especially dantrolene-Na fails.[11-13]

In the management of the post NMS patient, clinicians are advised to use the lowest doses of low potency neuroleptics or atypical antipsychotics. Clinicians should use minimal doses of antipsychotics with gradual increases and keep in mind the alternative classes of psychotropics.[7] In our case, antipsychotic drugs were re-initiated at the previous dose when all the major and minor signs disappeared. Since NMS developed after antipsychotic drug overdose in the present case, we thought it would be suitable to start the antipsychotic medication with the same dose he used previously instead of a lower dose.

Conclusion

Patients with antipsychotic drug overdose may present with NMS, sometimes resulting in cardiac arrest. Therefore, we believe that they should be treated in the ICU. Its unpredictable occurrence, clinical course, response to treatment and risk of recurrence are still a challenge to clinicians, suggesting that there is a need for great concern.

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