

Serotonin Syndrome Caused by Moclobemide – Clomipramine Interaction

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ABSTRACT:

SEROTONIN SYNDROME CAUSED BY MOCLOBEMIDE – CLOMIPRAMIN INTERACTION

The serotonin syndrome is due to serotonergic hyperstimulation, which is caused, mostly, by the interaction between a serotonergic agent and a serotonin-enhancing drug, in particular the monoaminooxidase inhibitors. A male patient, 21 years old, with presenting symptoms and findings as unconsciousness, flushing, diaphoresis, tremor, elevated body temperature, disseminated muscular rigidity and increased salivation is reported. In the ICU, supportive treatment were applied. After his conscious was normalized, the patient explained that he had taken 900 mg moclobemide and 150 mg clomipramine together to provide strong effect on his depression. This patient was accepted as serotonin syndrome and rhabdomyolysis related to this syndrome, induced by moclobemide plus clomipramine interaction. Also history, laboratory and clinical data confirmed the diagnosis of serotonin syndrome according to Sternbach's criteria. As we observed and as reported in the recent literature, the most significant adverse effects during anti-depressive therapy appear to be drug interactions between clomipramine and moclobemide which could be fatal.

Key words: serotonin syndrome, moclobemide, clomipramine, rhabdomyolysis, adverse effect.

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ÖZET:

MOKLOBEMİD – KLOMİPRAMİN ETKİLEŞİMİ NEDENLİ SEROTONİN SENDROMU

Serotonerjik hiperstimülasyonla oluşan serotonin sendromu en fazla serotonerjik bir ajan ve özellikle monoaminoksidaz inhibitörleri üzere serotonin arttırıcı bir ilaç arasındaki etkileşim nedeniyle ortaya çıkar. 21 yaşında bir erkek hasta, bilinçsizlik, kızarıklık, terleme, titreme, beden ısısında yükselme, yaygın müsküler sertlik ve artmış tükürük salgısı yakınma ve bulguları mevcuttu. Yoğun bakım ünitesinde destekleyici tedavi uygulandı. Daha sonra bilinci normale dönen hasta, depresyonuna etkisini güçlendirmesi için 900 mg moklobemid ve 150 mg klomipramini birlikte aldığını belirtti. Hastanın tanısı moklobemid ve klomipramin etkileşiminin neden olduğu serotonin sendromu ve bu sendromla ilişkili rabdomyoliz olarak kabul edildi. Keza anamnez, laboratuvar ve klinik veriler de Sternbach'ın kriterlerine göre serotonin sendromu tanısını doğruluyordu. Gözlemlediğimiz ve yeni literatürde bildirildiği kadarıyla, antidepresif tedavi sırasında en önemli yan etkiler moklobemid ve klomipramin arasındaki ölümcül olabilen ilaç etkileşimleri olarak görülmektedir.

Anahtar sözcükler: serotonin sendromu, moklobemid, klomipramin, rabdomyoliz, yan etki.

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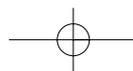
INTRODUCTION

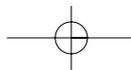
Serotonin syndrome is a potentially life-threatening complication of psychopharmacological drug therapy. The syndrome is produced most often by the concurrent use of two or more drugs that increase brainstem serotonin activity and is often unrecognized because of the varied and non-specific nature of its symptomatology. Serotonin syndrome is characterised by alterations in cognition, behavior, autonomic nervous system function and neuromuscular activity(1).

Case

A male patient, 21 years old, was brought to the emergency room and taken to the intensive care unit (ICU) with presenting symptoms and findings as unconsciousness, flushing, diaphoresis, tremor, elevated body temperature, disseminated muscular rigidity, increased salivation. On physical examination arterial blood pressure 150 / 90 mmHg, pulse 140 beats/minute, body temperature 39.7 °C, respiratory rate 28 per minute, midriasis, disseminated muscular rigidity, flushing, diaphoresis, increased

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salivation, hyperreflexia, mental status changes, agitation, incoordination, bilaterally Babinsky positivity were observed. Glasgow Coma Score was five point. He had been given moclobemide and clomipramine by different doctors and at different times for pharmacological therapy of depression. When he was found in his room, there were empty boxes of those drugs.

In biochemical examination, leukocyte count was 21300, urea was 68mg/dl, creatinine was 1.8 mg/dl, AST was 237 IU/L, ALT was 73 IU/L, CK was 15820 IU/L. Urine protein level 700 mg/dl, myoglobinuria 130000ng/ml, Na 145 mmol/L, arterial blood gases pH 7.47, pCO₂ 31mmHg, HCO₃ 22.9 mmol/L, osmolar gap 4 mosmol/L, PTT 12.7 sec, O₂ saturation 94% were observed. There was a sinus tachycardia on ECG and no foci were evidenced on the electroencephalogram. These results were supported to rhabdomyolysis. Changes on some laboratory examinations were illustrated in Table 1.

Table.1 Changes on laboratory findings

	WBC	Glucose mg/dl	Urea mg/dl	Cr. mg/dl	AST IU/L	ALT IU/L	CK IU/L	LDH IU/L
Feb. 18	21300	90	68	1.8	237	73	15820	1051
19	27200	95	64	0.7	1035	434	43500	3010
20	18600	88	45	0.7	1080	620	51400	3525
21	16200	-	39	0.7	1310	720	57800	4420
22	10400	85	26	0.8	1315	615	74460	2905
23	10200	-	-	-	970	550	57600	2480
24	9700	75	26	0.6	292	424	11225	1605
25	9400	-	-	-	78	208	1658	994

The patient was accepted as a serotonin syndrome induced by moclobemide plus clomipramine interaction. He had gastric lavage performed, monitored and supported with oxygen supplementation.

Sodium bicarbonate was administered (1 mmol/kg) in order to maintain urine pH above 6,5. Body temperature was lowered by cold compression and 10 mg benzodiazepine was applied intravenously for the relief of muscular rigidity. Fluids and mannitol infusion were applied in order to obtain hourly urine volume above 250 cc. The patient's conscious was normalised at the second day of admission. Plasma creatinine kinase enzyme was reached peak level of 74460 IU/L at the fifth day and it was diminished gradually. All laboratory parameters were near normal levels at the eleventh day. When the patient's

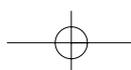
conscious was normalised, he reported that he had taken 900 mg moclobemide and 150 mg clomipramine together to provide strong effect to his depression.

DISCUSSION

The incidence of the serotonin syndrome is not known. Once treatment is instituted the syndrome typically resolves within 24 hours, but confusion can last for days, and death has been reported(2). Sternbach diagnostic criteria make it possible to diagnose serotonin syndrome in a wider range of patients but they sometimes make it difficult to make the differential diagnosis in the presence of certain limited symptoms. Sternbach proposed that coincident with the addition of or increase in a known serotonergic agent to an established medication regimen, at least three of the following clinical features should be present: changes in mental status,

agitation, myoclonus, hyperreflexia, diaphoresis, shivering, tremor, diarrhea, mental incoordination and fever (1). In contrast, the criteria of Dursun et al. may make a more accurate diagnosis possible, though only in severe cases (3).

Moclobemide is one of the new group antidepressants which is reversible inhibitor of MAO-A (RIMA) that has begun to be used in clinical psychopharmacology recently(4). Clomipramine is a tricyclic antidepressant characterised by inhibition of, especially, serotonin and mildly norepinephrine reuptake (18). Both drugs are similar according to their pharmacokinetic effects and cytochrome p450 hepatic enzymes. These enzymes are under genetic control and with polymorphism and the efficacy may be changeable. As these enzymes are interacted with drugs that elevated plasma levels, toxic effects or lower plasma levels and ineffective



response can be observed. Both drugs are metabolised by CYP2C19 enzyme. The other enzymes CYP1A2 and CYP2D6 responsible for clomipramine metabolism are inhibited by moclobemide (19). Moclobemide has been shown to have similar antidepressant efficacy to tricyclic antidepressants, selective serotonin re-uptake inhibitors and nonselective irreversible MAOIs. Comparative studies have established that moclobemide is better tolerated at therapeutic dosages and has less toxicity in overdose than TCAs and nonselective, irreversible MAO inhibitors(5). However, life threatening complication called Serotonin Syndrome caused by moclobemide can be seen rarely.

A wide range of substances were involved in 226 cases published worldwide since 1950 whenever there was any use of single or combined serotonimetic treatments. Of the 226 cases, 105 fulfilled the Sternbach criteria for serotonin syndrome. However, moclobemide, a RIMA, was represented in only 9 of the 226 published cases and 3 of the 105 defined serotonin syndromes, either in multi-drug combinations and/or in mixed drug overdose(1). RIMAs are potent inhibitors of MAO-A in the brain; they increase the free cytosolic concentrations of norepinephrine serotonin and dopamine in neuronal cells and in synaptic vesicles. Extracellular concentrations of these monoamines also increase. The case of moclobemide increases in the level of serotonin is the most pronounced (6,7). In multicentric study, 2300 patients were treated with moclobemide in doses up to 600 mg/day, without dietary restrictions, there was no tyramine related hypertensive reaction(8). The selective block of one of the isoenzymes does not stop the metabolism of tyramine because this toxic compound is metabolised by both isoenzymes (9). The drug is completely metabolised by the liver. Moclobemide is rapidly and completely absorbed following oral administration in a variety of dosages and forms. So liver disease causes a dra-

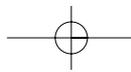
matic reduction in clearance, dosage must be adjusted for patients with liver disease(10). In our cases, hepatic first pass rate can be affected by drinking three glass of alcohol nearly twenty hours prior to the hospital, admission. Meanwhile, risky combination had occurred related with serotonin syndrome by taking 150 mg clomipramine with 900 mg moclobemide together. We don't know exact mechanism of interaction between moclobemide and clomipramine which is responsible for serotonin syndrome. It may be single drug affect, pharmacokinetic interaction, pharmacodynamic interaction or combined interaction. Further work is needed to establish the diagnostic criteria, incidence and predisposing factors.

No case of serotonin syndrome has been reported following ingestion of moclobemid alone. Indeed, overdoses of moclobemide alone induce generally mild and reversible signs of central nervous system and gastrointestinal irritation which do not need particular intervention (11,12,13) although as with other antidepressants mixed overdoses with moclobemide and other CNS-acting drugs could be life-threatening(14,15,16). There are some reports related with serotonin syndrome, induced by moclobemide-clomipramine interaction that may be fatal progress as reported in medical literature between 1993 and 1998. In many circumstances, serotonin syndrome has a nonfatal clinical course but in certain cases and for poorly understood reasons, clinical manifestations can include circulatory collapse, malignant hypertermia, convulsions and rhabdomyolysis. These forms are often fatal(17).

This medication must be employed with the utmost caution and a certain time interval should elapse before the introduction of a serotonergic agent. In this case, we want to attract attention on this serious interaction in ordinary psychopharmacologic practice.

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