HOSPITAL CHRONICLES 2013, 8(1): 31–33

CASE REPORT

Serotonin Toxicity Syndrome in Pregnancy: Could the Values of Blood Gases Be Affected?

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KEY WORDS: *pregnancy; serotonin; serotonin toxicity syndrome; blood gases*

Abbreviations
aPTT = activated partial thromboplastin time
Hbf = fetal hemoglobin
Hb = hemoglobin
INR = international normalized ratio
PO_2 = partial pressure of oxygen
SGOT = serum glutamic oxaloacetic transaminase
SGPT = serum glutamic pyruvic transaminase
SSRIs = selective serotonin reuptake inhibitors

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Manuscript received March 13, 2012; Revised manuscript received November 19, 2012; Accepted December 7, 2012

ABSTRACT

Serotonin toxicity syndrome is a potentially life-threatening condition caused by excessive serotonergic activity in the nervous system. It is characterized by mental status changes, autonomic instability, and neuromuscular hyperactivity. Critically ill patients may require neuromuscular paralysis, sedation, and intubation. If serotonin syndrome is recognized and complications are managed appropriately, the prognosis is favorable. In the present case, we discuss the clinical presentation and outcome of the serotonin syndrome which was developed in a 30-year-old pregnant woman with a medical history of depression managed by selective serotonin-noradrenaline reuptake inhibitors. This case is presented to inform physicians about our observations regarding the results of blood gases and to discuss a possible explanation.

INTRODUCTION

Serotonin syndrome is a toxic condition of the central nervous system which is due to the increased serotonergic activity in the spinal cord caused by the increased sensitivity of serotonin receptors.[1] Serotonin syndrome is induced by the use of pharmacologic agents that increase serotonergic activity. Serotonergic agents include medications that inhibit serotonin reuptake (selective serotonin reuptake inhibitors [SSRIs], tricyclic antidepressants), medications that increase serotonin release (amphetamines, opioid analgesics), agents that inhibit serotonin metabolism (monoamine oxidase inhibitors, linezolid), and post-synaptic serotonin receptor agonists (buspirone, carbamazepine).

Diagnosis is made based on clinical symptoms; no radiologic or laboratory method exists for diagnosis. Neuromuscular excitation (including clonus, myoclonus, tremor, and hyperreflexia), autonomic excitation (including fever, mydriasis, tachycardia, and tachypnea), changes in mental status (agitation and confusion), and changes in vital signs (fever, tachycardia, and hypertension) are the m ost important clinical symptoms. Leukocytosis, increased serum creatinine, elevated liver enzymes, and acidosis can be

Conflict of Interest / Financial Support: The authors hereby confirm that neither the manuscript nor any part of it has been published or is being considered for publication elsewhere. All the authors have seen, approved, and are fully conversant with this manuscript. Each of us acknowledges that he participated sufficiently in the work to take public responsibility for its content. There is no known to us conflict of interest. There is no financial support.

observed in some patients. The spectrum of serotonin toxicity extends from mild side effects, to severe coma that can result in death.[2,3] Herein we present a case of serotonin syndrome that was induced by the use of a SSRI. The most impressive finding was related to the results of blood gas values which we try to explain.

CASE PRESENTATION

A 30-year-old pregnant woman was admitted to the delivery room, at 30 weeks of gestation, due to pre-eclampsia and stained amniotic fluid. She had a past medical history of depression managed by selective serotonin-noradrenaline reuptake inhibitors (venlafaxine in dose 75 mg/day). Because of the very low heart rate of the fetus, the patient underwent an emergency caesarean section. A dead baby was delivered.

The patient was admitted to the intensive care unit for further support. The laboratory reports indicated elevated liver enzymes (SGPT: 537 U/L, SGOT: 298 U/L), renal failure (urea: 69 mg/dl, creatinine: 2.52 mg/dl), high leukocyte count (27.800/mm^3), platelet count of 140,000/mm^3, and hemoglobin level of 12.4 mmol/l. The coagulation profile was abnormal (INR: 1.66, aPTT: 46 seconds). She had a pulse rate of 85/min, respiratory rate of 18/min, blood pressure of 110/70 mmHg, temperature of 39˚C, and oxygen saturation of 99% on room air. She was neither fully alert nor oriented with Glasgow coma scale score of 10/15.

Half an hour later, the patient lost her consciousness. Physical examination revealed mild bilateral mydriasis, nystagmous, salivation, positive oculocephalic reflexes, presentation of stiff neck and lateralization in motor examination, active deep tendon reflexes, no Babinski reflex, flushing of the skin, tachycardia without arrhythmia, and severe hypertonicity. No additional pathological findings were observed. Both the psychiatric and neurological consultations recommended magnetic resonance imaging of the brain which was normal. Cardiology consultation revealed no cardiac problem. Toxicology blood tests revealed high venlafaxine levels (1551 μg/l, normal range: 195-400 μg/dl). The diagnosis of serotonin toxicity syndrome was established.[1,4] Patient's management included discontinuation of the responsible drug, supportive care, control of agitation, and treatment of autonomic dysfunction and hyperthermia.[5]

However, the most impressive findings were the results of blood gas analysis. In particular, the right radial artery and a left forearm vein were cannulated. In the first three hours following patient's admission, blood samples from both vessels (artery and vein) were received every one hour. Table 1 summarizes our findings. During the first two hours, the arterial and venous blood gas values were similar, but they started to differentiate by the time the third blood sample was taken. It was by that time when the patient started to get stabilized and the majority of her serotonin toxicity syndrome symptoms receded. From then onwards, the blood gas values were predictable, the patient was stable, and she was discharged in good health the following day.

DISCUSSION

The diagnosis of serotonin toxicity syndrome is suggested with a sensitivity of 84% and specificity of 97% by the Hunter

TABLE 1. Arterial and venous blood gas values during the first three hours after patient's admission

	1st hour		2nd hour		3rd hour	
	Arterial	**Venous**	**Arterial**	**Venous**	**Arterial**	**Venous**
pH	7.278	7.274	7.272	7.278	7.365	7.334
pCO_2	33.0 mmHg	30.3 mmHg	33.9 mmHg	32.9 mmHg	30.5 mmHg	37.0 mmHg
pO_2	133 mmHg	102 mmHg	114 mmHg	104 mmHg	125 mmHg	46.4 mmHg
Hb	12.5 g/dl	15.1 g/dl	12.8 g/dl	13.1 g/dl	12.2 g/dl	12.7 g/dl
SpO_2	99%	97.4%	98%	97.8%	98.8%	86%
FCOHb	0.6%	0.3%	0.6%	0.7%	0.6%	0.7%
FHHb	1.0%	2.6%	2.0%	2.2%	1.2%	13.8%
FMetHb	0.7%	0.6%	0.7%	0.7%	0.7%	0.8%
FO_2Hb	97.7%	96.5%	96.7%	96.4%	97.5%	84.7%
HCO_3	14.9 mmol/l	13.6 mmol/l	15.1 mmol/l	14.9 mmol/l	17.0 mmol/l	19.2 mmol/l

FCOHb = fraction of carboxyhemoglobin; FHHb = fraction of deoxyhemoglobin in total hemoglobin; FO_2Hb = fraction of oxyhemoglobin; FMetHb = fraction of methemoglobin; Hb = hemoglobin; HCO_3 = bicarbonate; pCO_2 = partial pressure of CO_2; pO_2 = partial pressure of oxygen; SpO_2 = oxygen saturation.

serotonin toxicity criteria in the presence of a serotonergic agent and one of the following symptoms: spontaneous clonus, inducible clonus and agitation or diaphoresis, ocular clonus and agitation or diaphoresis, tremor and hyperreflexia, hypertonia and temperature >38˚C, and ocular clonus or inducible clonus.[2] The Hunter criteria have not been validated in patients who develop serotonin toxicity on therapeutic doses of serotonergic agents. In our patient, elevated liver enzymes, renal failure, leukocytosis, and high temperature were observed. Furthermore, physical examination revealed nystagmous, salivation, positive oculocephalic reflexes, presentation of stiff neck and lateralization in motor examination, active deep tendon reflexes, flushing of the skin, tachycardia, and severe hypertonicity.

The management of this syndrome varies depending on the severity of symptoms and includes removal of responsible medications, supportive care, cyproheptadine (a 5-HT_{2A} antagonist), control of agitation (with benzodiazepines, such as lorazepam), and treatment of autonomic dysfunction and hyperthermia.[6] With appropriate management, symptoms resolve within 24 hours in about 60% of all cases, but drugs with longer duration of action or active metabolites may cause prolonged symptoms.[1]

In this case, the possible scenarios to explain all the observations according to blood gas results could be the following. Firstly, the occurrence of an arteriovenous malformation which in our case is not possible as this phenomenon was observed for a limited period of time. Secondly, the findings could have been the result of serotonin toxicity syndrome, a scenario supported by the fact that this phenomenon was observed in time relevance with this syndrome's symptoms. However, there are no literature references or other authors' similar observation to advance this point of view. Finally, blood gas findings could have been caused by a large amount of fatal hemoglobin (Hbf - no ability to measure it) retrograded through the umbilical cord to mother's circulation. Hbf represents the 80%-85% of total Hb in term fetus and has a close chemical relationship with O_2, committing more amount of O_2 than the Hb, even in cases of low PO_2.[2] Hbf does not easily release O_2, resulting in elevated PO_2 levels in mother's venous blood.

CONCLUSION

Serotonin toxicity syndrome is a potentially life-threatening condition. Educating patients, family members, and caregivers about these side effects increases the chance of early diagnosis and immediate intervention and reduces the risk of death. Furthermore, physicians need to be aware of these probable risk factors when prescribing antipsychotic treatment. Finally, more studies, continued analysis, and further investigation are needed to determine if there is any relationship between the serotonin toxicity syndrome and abnormal blood gas values in pregnancy. According to the present case, the only logical assumption to be made is that blood gases might be changed during the acute phase of serotonin toxicity syndrome - time relevance deserves an organized attempt to replicate findings.

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