The Libyan International Medical University

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Effect of selective serotonin reuptake inhibitors and Monoamine Oxidase inhibiter in Serotonin syndrome

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Abstract :

Serotonin syndrome (SS) is a consequence of the interaction between serotonergic agents and monoamine oxidase inhibitors. The most frequent clinical features are changes in mental status. Its effect in the brainstem and spinal cord on specific type of the serotonin (5-hydroxytryptamine, or 5-HT) receptor. Both sexes have been affected, and patients' ages have ranged from 20 to 68 years. stoppage of the suspected serotonergic agent and institution of supportive measures are the primary treatment. Once treatment is beginning the syndrome naturally resolves within 24 hours, but confusion can last for days and death in some cases. Conclusions: The serotonin syndrome is a toxic condition requiring heightened clinical awareness for prevention, recognition, and prompt treatment. Further work is needed to establish the diagnostic criteria, incidence, and predisposing factors, to identify the role of 5-HT antagonists in treatment, and to differentiate the syndrome from the neuroleptic malignant syndrome(1)(2).

Introduction :

serotonin (5-hydroxytryptamine, 5-HT) is produced from brainstem raphe nuclei consist of nine nuclei that produce serotonin, forming an inferior caudal group, which sends excitatory axons to the spinal cord and medulla (descending pathways), and a superior rostral group, from which ascending projections (ascending pathways) inhibit thalamic and cortical regions. It has been postulated that ascending pathways are associated with sleep and synchronization of cortical neurons, whereas descending rant nociceptive-type pathways, when stimulated, result in inhibition of neurons in the spinothalamic tract and cause analgesia cant cross the blood-brain barrier, it had many functions in centrally and peripherally neurons in nerve system such as in the peripheral nervous system (PNS) includes vasoconstriction via smooth muscle stimulation, platelet aggregation, uterine contraction, intestinal peristalsis, and bronchoconstriction; and in central nervous system (CNS) has effects on controlled behavior, attention, affect, cardiorespiratory function, pain perception, aggression, motor control, temperature, sleep, appetite, and sexual function. Platelets use an uptake pump to scavenge serotonin produced by the intestinal enter chromaffin cells, the only peripheral source of serotonin. Overproduction of serotonin can be caused by interaction between drugs That result by using two or more of serotonin–elevation drug such as serotonin reuptake inhibitor (SSRI) and monoamine oxidase inhibitor (MAOI).1it's a probable outcome of extra serotonergic ageism of central nervous system (CNS) receptors and peripheral serotonergic receptors, extra serotonin makes some deferent manifestation that caused the serotonin syndrome is excess serotonin at the synapse, usually consists of a triad of symptoms including cognitive-behavioral changes, neuromuscular excitability, and

autonomic instability, Agitation, mental status changes (confusion, hypomania), myoclonus, shivering, tremor, hyperreflexia, ataxia, diarrhea or fever. that all caused by increase in dosage or addition of serotonergic agents and other possible etiologies, for example, metabolic disorder, or substance intoxication or withdrawal Serotonin Syndrome and Other Serotonergic Disorders thrombocytopenia, tonic-clinic seizures, multiorgan failure, rhabdomyolysis with resultant hyperkalemia, renal failure, and acidosis, and finally, respiratory failure and/or aspiration pneumonia due to rigid thoracic muscle. So the differential diagnosis usually includes neuromuscular malignant syndrome (NMS), sepsis with meningitis, delirium tremens (3)(4)(2)**.**

Aim:

The serotonin syndrome(SS) is result from collaboration between 2 drugs such as serotonergic agents and monoamine oxidase inhibitors. its made-up specific pathogeneses in central nerve system (CNS) stimulation of the(5-TH1A) is some forms of 5-TH receptor. Termination of the suspected serotonergic agent and establishment of understanding events are the primary treatment . they needed to found the diagnostic principles, frequency, and affecting factors, to find the role of 5-HT antagonists in treatment, anticholinergic toxicity, heatstroke, and sympathomimetic overdose. Historical and lab data are crucial to rule out these other disorders.

Materials and Methods:

This review describes the presentation and management of serotonin syndrome and discusses the drugs and interactions that can precipitate this syndrome with the goal of making physicians more alert and aware of this potentially fatal yet preventable syndrome(5).

Result :

Serotonin is a neurotransmitter that has more than one type of vital functions that affect the nervous system, usually an imbalance occurs in the absorption and cracking of Serotonin in the body as a result of the interaction of two types of drugs such as antidepressants and monoamine oxidase inhibitor, these disorders occur for those who suffer from psychological problems not It must necessarily be severe, and also with those who take tramadol as a treatment or addiction. However, it is easy to treat this condition by stopping this medication, the patient will have symptoms of withdrawal,

usually it is controlled by giving reduced doses of the medication, but it is possible The patient dies from these withdrawal symptoms(2)(5).

Discussion :

The synthesis of serotonin begins when ingested tryptophan crosses the blood-brain barrier via a nonspecific amino acid transporter and enters neurons to be hydrolyzed and subsequently decarboxylase to serotonin, in storage vesicles ready for release into the synaptic cleft of the presynaptic neuron(2). There are presynaptic and postsynaptic receptors, the stimulation of the former turning off the further release of serotonin and the latter, with summation at the hillock, affecting depolarization of the axons that run to terminal fields in the cortex, thalamus, medulla, and spinal cord. Serotonin is removed from the cleft via reuptake pumps and is either repackaged into storage vesicles or degraded by monoamine oxidase (MAO), which is present on the mitochondrial membrane, into 5-hydroxy indole acetic acid (5- HIAA). There are two isoforms of MAO: MAO-A preferentially metabolizes serotonin and MAO-B is more prevalent in the brain and postulated to "clean up" catecholamine's, which have the ability to "contaminate" the vesicles containing serotonin(3).

The serotonin system has the largest number of receptors and subtypes of any of the neurotransmitter systems include 5-HT1 (subtypes A, B, C, D, E, F), 5-HT2 (subtypes A, B, C), 5-HT3, and 5-HT4, although there are many other types are currently being investigated (5-HT5, 5-HT6, 5- HT7) [4]. 5-HT1B and 5-HT1D are recognized as species homologs of the same receptor subtype, 5-HT1A receptors seem to play a central role in depression and anxiety. 5-HT1D receptors are found primarily in the cephalic blood vessels and play an important role in the pathophysiology of migraine headaches. 5-HT2 receptors are located in the brain as well as peripherally in the large arteries and veins, mediating vasomotor tone. Of these subtypes of 5-HT2, 5-HT2A and 5-HT2C are found in the brain, whereas 5-HT2B exists in the gastrointestinal (GI) system, uterus, and vascular endothelium / smooth muscle. 5-HT3 receptors, located in proximity to the emesis center, are believed to be involved in emesis and are targeted by the antiemetics, including ondansetron and metoclopramide. Finally, the GI tract is rich in 5-HT4 receptors, which modify peristalsis(3)(2)(5).

So the inter action between serotonin reuptake inhibiter that work as reduced serotonin metabolism increased serotonin synthesis, increased serotonin release, activation of serotonergic receptors, and inhibition of certain cytochrome P450 (CYP450) enzymes by the SSRIs themselves, including CYP2D6 and CYP3A4. This inhibition results in the accumulation of many serotonergic drugs (venlafaxine, methadone, tramadol, dextromethorphan), that are usually metabolized by these

enzymes, creating an exacerbation loop in which the SSRI inhibits the metabolism of a certain drug, which in turn increases serotonergic activity. Ciprofloxacin has been reported to cause serotonin syndrome via its CYP3A4 inhibition. Some cases caused by the concomitant use of citalopram and fluconazole suggested that the inhibition of CYP2C19 by fluconazole resulted in the accumulation of its substrate citalopram(4)(5).

The most acute manifestation of excess serotonin at the synapse, usually consists of a triad of symptoms including cognitive-behavioral changes, neuromuscular excitability, and autonomic instability, the diagnosis is made on clinical grounds alone, and there is a broad range in both the severity of presentation and the constellation of symptoms observed, and hence mild, atypical cases are very likely to be missed or mistaken for worsening psychiatric or neurological illnesses. 1 usually characterized by excitation, but coma does occur. Autonomic instability involving diaphoresis, mild elevations in temperature, hypertension, and tachycardia is commonly seen. Less often, hypotension can occur, in severe cases, muscular rigidity can lead to progressive hypoventilation with ensuing cyanosis(3)(2).

Life-threatening complications can include disseminated intravascular coagulation, leukopenia, Serotonin Syndrome, tonic-clonic seizures, multiorgan failure, rhabdomyolysis with resultant hyperkalemia, renal failure, and acidosis, and finally, respiratory failure and/or aspiration pneumonia due to rigid thoracic muscles. Lab tests are not useful for the diagnosis of serotonin syndrome. in some time occasionally, abnormal lab findings can include mildly elevated muscle creatine kinase levels in correlation with the degree of muscle rigidity, a mild elevation in liver enzymes with associated hyperammonemia, abnormally low or high white blood cell counts, and EEG findings of diffuse slowing consistent with a diffuse metabolic encephalopathy.The differential diagnosis usually includes neuromuscular malignant syndrome (NMS), sepsis with meningitis, delirium tremens, anticholinergic toxicity, heat stroke, and sympathomimetic overdose. Historical and lab data are crucial to rule out these other disorders(5)(4).

The treatment of serotonin syndrome is primarily supportive, consisting of dialysis in the case of lithium overdose. Usually the syndrome resolves with discontinuation of the serotonergic medications alone, with 70% of patients recovering within 24 hours, 40% requiring ICU admission, and 25% requiring intubation [6]. Treatment recommendations for more severe cases are based on case reports only. Accordingly, benzodiazepines are first-line treatments to decrease myoclonus and the muscle rigidity that can lead to respiratory compromise and rhabdomyolysis, and are particularly indicated if severe agitation is present or if seizures appear to be imminent(3).

Failure of benzodiazepines to decrease muscular rigidity calls for the immediate use of nondepolarizing paralytic agents. Beta-blockers with 5-HT1A-receptor blocking properties, that is, propranolol and pindolol, show some promise in reversing some of the neuromuscular and autonomic complications and are especially useful if tachycardia and/or hypertension are present. Additionally, nonspecific 5-HT2 blockers, including methysergide and cyproheptadine, have been used with varying success, given the theory that a disturbance in the balance between dopaminergic and serotonergic systems leads to serotonin syndrome. However, in addition to dopaminergic blockade, phenothiazines also block 5-HT2 receptors and likely improve the symptoms of serotonin syndrome via this mechanism (2)(4)(5).

Conclusion:

Serotonin syndrome is increasingly common but not well recognized by physicians. The physicians should consider the possibility of serotonin syndrome in patients taking serotonergic drugs who present with autonomic or mental status changes and neurological findings. The findings of clonus, ocular clonus, hyperreflexia, and hypertonicity should prompt evaluation and medication review. Treatment is based on severity and focuses on prompt cessation of offending agents, treatment of hyperthermia, and use of benzodiazepines to decrease hypertonicity and neurological excitability. The use of 5-HT antagonists should be considered in moderate and severe cases. Increased awareness and monitoring of patients beginning treatment with antidepressants can decrease the risk of worsening anxiety, agitation, and possibly suicide(4)(5).

Reference:

1. Mills KC. Serotonin syndrome. Vol. 52, American Family Physician. 1995. p. 1475–82.
2. Rose CZ. Serotonin syndrome. Cleve Clin J Med. 2017;84(5):342.
3. Volpi-Abadie J, Kaye AM, Kaye AD. Serotonin syndrome. Ochsner J. 2013;13(4):533–40.
4. Kelly CM, Juurlink DN, Gomes T, Duong-Hua M, Pritchard KI, Austin PC, et al. Selective serotonin reuptake inhibitors and breast cancer mortality in women receiving tamoxifen: A population based cohort study. BMJ. 2010;340(7742):355.
5. Zagaria MAE. Serotonin syndrome. Vol. 32, U.S. Pharmacist. 2007. p. 20–3.