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A Dangerous Triad: Sertraline, Mirtazapine and Methadone

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Abstract

Serotonin syndrome is a potentially life-threatening complication of using serotonergic agents. Mirtazapine is a relatively safe antidepressant and has a comparatively low incidence of side effects but can induce serotonin syndrome in combination with other serotonergic agents such as methadone and sertraline. We describe a 41-year-old man with a history of heroin misuse and depression. He developed symptoms indicative of serotonin syndrome during his ICU stay. The serotonin-related symptoms resolved soon after withdrawal of mirtazapine and sertraline combined with supportive measures. After receiving appropriate supportive treatment, his general condition recovered and he was discharged without any neurological sequelae. With the increasing use of serotonergic agents, awareness of serotonin syndrome is important. Early diagnosis and timely discontinuation of the offending agent(s) are imperative to prevent morbidity and mortality.

Keywords

Sertraline, Mirtazapine, Methadone, Serotonin syndrome

Introduction

Serotonin syndrome is a serious and life-threatening toxic reaction firstly reported in the 1950's in patients taking a monoamine oxidase (MAO) inhibitor called iproniazid in combination with pethidine. It was theorized that the reaction was due to over-stimulation of 5-hydroxytryptamine (5-HT) receptors in the central nervous system due to the combined effects of the drugs. Nowadays, it is known that the serotonin syndrome is mediated primarily by the postsynaptic 5-HT1A receptors and secondarily by the 5-HT2A receptors either at the central nervous system (CNS) or peripherally, occurring exceptionally after taking only one drug but, more commonly when two or more serotonergic drugs act in concert [1]. The pharmacological mechanisms causing serotonin syndrome include: Increase in serotonin synthesis, inhibition of serotonin metabolism, increase in serotonin release, inhibition of serotonin uptake, activation of serotonergic receptors and hypersensitivity of the postsynaptic receptors [2]. This hyperstimulation of the serotonin receptors at the CNS results in a central altered expression (agitation, hyperreflexia, myoclonus, mental status changes, etc.), combined with a myriad of signs and symptoms by this effect on the receptors present on platelets and smooth muscle (platelet aggregation, vasoconstriction, bronchoconstriction, diaphoresis, diarrhea, etc.) [3] (Table 1).

Table 1: Therapeutic groups that can cause serotonin syndrome [4].

Therapeutic group	*Medication examples*
SSRI antidepressants	Fluvoxamine, paroxetine, **sertraline**
Miscellaneous	Lithium, trazodone, **mirtazapine**
Opioids	Pethidine, tramadol, **methadone**
Tricyclic antidepressants	Clomipramine, imipramine, amitriptyline
Parkinson's disease treatment	Selegiline, rasagiline, levodopa
Antibacterials	Linezolid
Anti-cancer drugs	Procarbazine
Anticonvulsants	Carbamazepine, valproate
Antiemetics	Metoclopramide, ondansetron, granisetron
Antihistamines	Chlorphenamine
Antimigraine drugs	Rizatriptan, sumatriptan, zolmitriptan
Anti-smoking aids	Bupropion
Anxiolytics	Buspirone
Diagnostic dye	Methylthioninium chloride
Herbal products	St John's wort

The constellation of symptoms characteristic of the serotonin syndrome fall into the three main areas of: Altered mental status, autonomic dysfunction and neuromuscular abnormalities [5]. The symptoms form part of the 'Sternbach diagnostic criteria' named after Dr. Harvey Sternbach who suggested that at least three of these features need to be seen before classifying this toxic reaction as serotonin syndrome rather than neuroleptic malignant syndrome. The initial criteria have been further developed into the Hunter Serotonin Toxicity Criteria [6]; the presence of a serotonergic agent plus one of the following:

- Spontaneous clonus.
- Inducible or ocular clonus and agitation or diaphoresis.
- Tremor and hyperreflexia.
- Hypertonia and hyperpyrexia (temperature exceeding 38 °C) and ocular or inducible clonus.

Conditions such as anticholinergic toxicity and neuroleptic malignant syndrome can be confused with serotonin toxicity. In the case of neuroleptic malignant syndrome, the symptoms of bradykinesia and extrapyramidal rigidity appear gradually over a period of several days and differ from those of serotonin toxicity where hyperkinesia, hyperreflexia, and clonuses predominate. The serotonin syndrome is a dose-related phenomenon that can develop shortly after the addition of a second serotonergic drug, or

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Table 2: Case reports involving mirtazapine induced serotonin syndrome.

Author(s)	Medications	Key symptoms	Treatment	Clinical outcome(s)
Demers, et al. [11]	Mirtazapine and fluoxetine	Tremor, restlessness, flushing and diaphoresis	Discontinuation of medication	Complete recovery
Hernandez, et al. [12]	Mirtazapine alone	Hypertension, altered mental state, myoclonus and hyperreflexia	Discontinuation of medication	Recovery with mild persistent rigidity
Duggal, et al. [13]	Mirtazapine, olanzapine and tramadol	Confusion, tachycardia, tremors, ataxia, hyperreflexia and myoclonus	Discontinuation of medication	Complete recovery
Houlihan, et al. [14]	Mirtazapine, tramadol and venlafaxine	Tachycardia, altered mental state, myoclonus and hyperreflexia	Discontinuation of medication	Complete recovery

replacement of the primary serotonergic drug without a sufficient washout period. The problem usually resolves within a period of 24 hours if the causative drugs are withdrawn and supportive measures are provided. It is important to recognize serotonin toxicity early due to the potential for rapid deterioration. Precipitating drugs should be stopped, with the consideration that extended release preparations may cause extended side effects. The mainstay of treatment is supportive care with agitated patients benefitting from the use of a benzodiazepine. Serotonin antagonists such as cyproheptadine or chlorpromazine are also options, with chlorpromazine used cautiously if the patient is hypotensive [7].

Case Report

A 41-year-old man with a past medical history of heroin misuse and depression treated with methadone, sertraline and mirtazapine, was admitted to hospital with a severe bronchospasm interpreted as an exacerbation of chronic obstructive pulmonary disease versus life threatening asthma. His condition deteriorated requiring noninvasive ventilation managed in the intensive care unit (ICU). During his stay in the ICU, he developed a clinical picture that was initially thought to be related to methadone abstinence: hypertension (185/95 mmHg), tachycardia (130 bpm), confusion, akathisia, profuse diaphoresis and hyperthermia (38.5 ˚C). Despite being well treated with methadone at his regular doses, a minutious neurological examination revealed confusion and mutism but obeying simple commands, generalized spontaneous myoclonus including ocular clonus without any physical stimulus, ataxia and muscular spasms alternating with hyperreflexia. His medications were reviewed. His use of Mirtazapine 15 mg once daily and Sertraline 100 mg once daily, which had been prescribed for depression in a last admission two months ago, were discontinued. Complete cessation of mirtazapine and sertraline resulted in a clinical resolution in 72 hours under treatment with clonidine and lorazepam. He was discharged from hospital with methadone and aripiprazole, as a partial agonist at D2 receptor trying to cause the minimal effect on serotonin receptors, with a follow up by his psychiatrist after hospitalization in order to have his mood reviewed.

Discussion

A number of case reports describe the development of serotonin syndrome after the addition of opiateanalgesics, such as oxycodone, pentazocine, and morphine, to a serotonin-specific reuptake inhibitor (SSRI). Our patient's admission drug regimen was notable for including three potent serotonergic agents: methadone, sertraline (SSRI) and mirtazapine [8]. All these three partially depend upon the P450 3A4 isoenzyme for effective metabolism and clearance. In addition to raising our patient´s serotonin via re-uptake inhibition, there may also have been an element of competition for CYP450 3A4 causing a reduction of metabolism of the drugs and prolongation of the toxic effects [9]. *In vitro* receptor assays by Codd, et al. [10] have identified methadone an opiate with significant serotonin re-uptake inhibitor activity. The assays identified the usual serotonin transporter affinity (Ki) for an SSRI as 0.13-2.2 with a lower value corresponding to a greater potency. Methadone was identified as having a Ki value of 14.1 indicating a relatively high potency compared to other opiates such as morphine with a Ki value of > 100,000; however, the methadone possibly was not the triggering drug because he was taking it for years. Possibly Mirtazapine, which has noradrenergic and specific serotonergic activity, was the precipitant of the syndrome because it was added in a previous admission. Differing with the sudden typical presentation of the serotonin syndrome, in this case, the patient suffered progressive deterioration in at least a month, and was the bronchospasm what precipitated the critical episode. Multiple cases of mirtazapine associated serotonin syndrome, due to either mirtazapine monotherapy or combined therapy with other drug(s), have been documented in the literature as identified in the table below (Table 2).

Conclusion

The use of serotonergic agents in clinical practice has increased in recent years, especially for the treatment of depression and chronic pain. As a result, serotonin syndrome will be more often encountered and awareness of this potentially life-threatening toxic effect is important to physicians. A detailed medication history along with careful observation of the clinical presentation should ensure prompt diagnosis of serotonin syndrome especially in combination of this tree drugs. Early identification of this syndrome, timely discontinuation of the offending agent(s), and adequate supportive treatment can prevent morbidity and mortality.

Ethical Statement

The authors declare that there are no conflicts of interest.

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