Myoclonic encephalopathy associated with the use of indomethacin.

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Abstract

According to World Health Organization, neurologic disorders affect over 1 billion people worldwide, constituting 12% of the global burden of disease, and this number is not static. Here we present a case of a 49-year-old male presented to the ER after being referred from a local hospital with the complaint of convulsion followed by prolonged altered sensorium. Our case report has noteworthy similarities with the scientific literature published before.

Keywords: Neurologic disorders, Myoclonic encephalopathy, Convulsion, Neurotransmitters, Indomethacin.

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Introduction

The emergence of new neurologic side effects of drugs worsens the challenges that neurologists face while prescribing medicines. These side effects can result in potential misdiagnoses, including false psychiatric diagnoses, as seen in some drugs. Certain unanticipated and unpredictable drug interactions can result in a confusing range of symptoms that may altogether be identified as a new medical condition. For instance, Serotonin Syndrome is a known adverse effect caused by overuse of drugs such as MAOIs, TCAs, SSRI, SNRI, Triptans, Tramadol, Lithium, Valproate to name a few [1]. Often, it is difficult to determine whether a neurologic condition is caused by a drug. The most difficult aspect in such cases is ensuring the specificity of the event related to the drug by ruling out other potential causes of the disorder. This is particularly true of less severe presentations of serotonin syndrome, which still contribute to patient morbidity [2]. Physicians are encouraged to consider the possibility of serotonin like syndrome in patients who present with autonomic changes, mental status changes, and neurological hyperexcitability despite of being on medications that are not known to cause Serotonin Syndrome. Here we present to you one such rare interaction of Indomethacin causing Serotonin like syndrome with minimal dose.

Case Report

A 49-year-old male presented to the ER after being referred from a local hospital with the complaint of convulsion followed by prolonged altered sensorium. There was no history of fever, cough in the recent past nor is he a known epileptic, as reported by next of kin. The course of management at the local hospital stated, administration of intravenous fluids and Inj. Eptoin 500 mg. Following which a CT Brain (Plain) was done and concluded, Normal. When brought to the ER, his GCS was 9 (E3 V2 M4). He had no episodes of convulsions since the one on the previous day, but was delirious. There was no myoclonus and movements were present. He was admitted in ICU. MRI Brain (Plain + Contrast) done was Normal. CSF study showed elevated proteins (83), elevated glucose (85), HGT at time of LP 122, elevated cells (8-all lymphocytes), RBC 1670. Blood Culture provisionally showed GPCs, reported on 3 days later showed MRSA and sensitive to Gentamycin, Tetracycline, Doxycycline, Ciprofloxacin, Levofloxacin, Clindamycin, Chloramphenicol, Linezolid and Tobramycin. He was started empirically on Inj. Monocef 2 gm TDS, Inj. Vanco 1 gm TDS, Inj. Acyclovir 750 gm TDS for 5 days and anti-epileptics i.e. Inj. Levipil 1 gm TDS, Inj. Eptoin 100 mg TDS. He improved in sensorium within 2 days and was shifted out of ICU on 4th day of hospitalization.

He complained of swelling and tenderness of both ankles which was reviewed by Orthopedic Surgeon and diagnosed as reactive arthritis. He was started on T. Indomethacin 25 mg TDS from 5th day of admission. He developed delirium from the next day and became restless, aggressive (punching people). In the next 24 hours, he became mute, irritable and developed myoclonus. He was not eating or speaking. He did not improve with Olanzepine. On examination, he was awake, confused, agitated, had akinetic rigidity and did not respond to verbal commands. He was afebrile and had opsoclonus, photophobia, intermittent clenching of teeth, multifocal myoclonus especially of face, eyelids, limb and trunk that increased on touching, moving limbs. He was unable to close his eyes. No aerophobia, hydrophobia noted. He had profuse sweating of forehead and body, but pupils were normal, heart rate 83 bpm and blood pressure 130/84 mm of Hg i.e. no signs of any autonomic instability were noted. He had mild neck, limb rigidity and clonus in ankles. DTJ UL 3+, LL 3+, plantar reflexes were withdrawal. His investigations revealed normal hemogram, renal function, liver function, CPK, antithyroid antibodies, thyroid profile, ANA negative. His post contrast MRI was normal. EEG showed occasional sharp waves and no evidence of non-convulsive status epilepticus. Repeat CSF study was done, and it showed persistent elevated proteins but not RBCs/cells. Repeat Blood Culture tested Negative. The patient improved slowly when Indomethacin was stopped and on administration of Lorazepam for 7 days.

Discussion

Cochrane Database of Systematic Reviews, PubMed, and Google were searched from January 1960 to December 2012 for articles on neurological effects of indomethacin, indomethacin psychosis, and serotonin syndrome, serotonin toxicity. Although there are a few research papers on Serotonin Syndrome, but hardly any on serotonin like syndrome induced

by indomethacin. No guidelines or consensus statements have been published for either diagnosis or management. Recommendations were drawn from the literature, but there is minimal high-level evidence, especially in the realm of treatment. Patient initially had MRSA sepsis for which he was treated with antibiotics and was being considered to be discharged. However, he suddenly developed altered sensorium with akinetic rigidity, mute with multifocal myoclonus without fever, hyperCKemia or marked autonomic dysfunction. He was suspected to have Serotonin Syndrome, but no obvious agent i.e. antidepressant/anti emetics were used prior to this development [1] (Table 1).

Neuroleptic malignant syndrome (NMS) bears some resemblance to serotonin syndrome, with similar symptoms of fever, mental status changes, and altered muscle tone [3,4] (Table 2).

Neuroleptic Malignant Syndrome, Hashimoto's Encephalitis, Rabies were ruled out by tests and history review [5] (Table 3).

On review of charts and medical literature, it became obvious that starting of Indomethacin was temporally related to development of Serotonin Syndrome (Indomethacin related Psychosis). Even though Indomethacin is not well known to develop CNS reactions and hasn't been established in the list of drugs causing Serotonin Syndrome [6-10] (Table 4).

The vast majority of serotonin (90%) is synthesized in the periphery, but brain serotonin levels are the main factor in development of serotonin toxicity. On the other hand, Indomethacin is a non-steroidal anti-inflammatory drug (NSAID) that has antipyretic and analgesic properties which is used to treat acute and chronic pain, primarily of neurological, rheumatic and orthopedic origin. The exact mechanism of action hasn't been established. However, it is believed that Indomethacin works by inhibiting the enzyme cyclo-oxygenase (COX-2) of the two distinct isofroms COX1, COX2 [11]. Prostaglandins sensitize afferent nerves and potentiate the action of bradykinin in inducing pain. Moreover, prostaglandins are known to be among the mediators of inflammation. Since Indomethacin is an inhibitor of prostaglandin synthesis, its mode of action may be due to a decrease of prostaglandins in peripheral tissues [12]. It is used to treat reactive arthritis, hemicranias continua, ankylosing spondylitis etc. to name a few. Depending on the dosage, studies show mild to severe adverse effects (mainly, gastrointestinal) in among eight to thirty seven percent of cases [13]. The exact mechanism of indomethacin causing psychosis is unclear. However, the molecular structure of indomethacin and serotonin are alike, as both of them have an indole moiety, which may explain the development of psychosis [14]. Some studies suggested effects on prostaglandins and neurotransmitters [15]. There is also evidence of decreased cerebral blood flow with indomethacin, which coincides with its peak levels and hence may contribute to adverse CNS effects [16].

Our case report has noteworthy similarities with the scientific literature published before. However, our case is unique as the

Table 1. *Signs and symptoms of serotonin syndrome.*

Seriousness	Autonomic Signs	`Neurological Signs	Mental Status	Other
Mild	Afebrile or low-grade fever	Intermittent tremor	Restlessness	-
	Tachycardia	Akathisia	Anxiety	
	Mydriasis	Myoclonus		
	Diaphoresis or shivering	Mukd hyperreflexia		
Moderate	Increased tachycardia	Hyperreflexia	Easily startled	Rhabdomyolysis
	Fever (up to 41 °C)	Induciblr clonus	Increased confusion	Metabolic Acidosis
		Ocular clonus (slow continuous lateral eye movements0	Agitation and hypervigillance	Renal failure
	Diarrhoea with normal skin colour	Myoclonus		Disseminated intravascular coagulopathy (secondary to hyperthermia)
Severe	Temperature often more than 41°C (Secondary to increased tone)	Increased muscle tone (lower limb>upper)	Delirium	As above
		Spontaneous clonus	Coma	
		Substantial myoclonus or hyperreflexia		

Table 2. *Criteria for guidance in diagnosis of NMS. The presence of all three major, or two major and four minor manifestations indicates a high probability of the presence of NMS, if supported by clinical history (e.g.. Not indicative of malignant hyperthermia) [5].*

Category	Manifestations
Major	Fever, rigidity, elevated creatine phosphokinase concentration
Minor	Tachycardia, abnormal arterial pressure, tachypnea, altered consciousness, diaphoresis, leucocytosis

Table 3. *Decision rules for diagnosing serotonin syndrome in the presence of serotonergic agents within the past 5 weeks: Hunter serotonin toxicity criteria.*

In the resence of 1 or more serotonergic drugs (within the past 5 weeks)	Yes, they have serotonin syndrome or toxicity
If patients have spontaneous clonus	Yes
If patients have inducible clonus and either agitation or diaphoresis	Yes
If patients have ocular clonus and agitation or diaphoresis	Yes
If patients have tremor and hyperreflexia	Yes
If patients are hypertonic and have a temperature > 38°C and have ocular clonus or inducible clonus	Yes

Table 4. *Drugs causing serotonin syndrome.*

Mechanism	Drugs causing serotonin toxicity without drug interaction	Drug combinations causing moderate to severe toxicity
Increased production of serotonin	L-Tryptophan	L-Tryptophan with MAOI
Increased serotonin release from neurons [7]	Amphetamines	Amphetamines and MAOI
	NMDA	NMDA and MAOI
NMDA and SSRI (lower risk)		
5-HT1A Antagonism[7]	Buspirone	Paroxetine and Buspirone
LSD		
Decrease serotonin reuptake	SSRIs	Analgesics with MAOI or SSRI
	Venlafaxine	Clomipramine with MAOI
	Clomipramine, imipramine	SSRIs, Venlafaxine with MAOI
	Tramadaol, meperidine, methadone, fentanyl	SSRIs, Venlafaxine, Buproprion
	Dextromethorphan	
	St John's wort	
MAO Inhibition[9,10]	MAOIs	Moclobemide and SSRIs or venlafaxine
	Selegiline	Irreversible MAOIs with all serotonergic drugs
	Linzolid	Linezolid and SSRIs
Uncertain	Lithium	-

5-HT1a: Serotonin 1A Receptor; LSD:nLysergic Acid Diethylamide; MAO: Monoamine Oxidase; MAOI: Monoamine Oxidase Inhibitor; NMDA: N-Methyl-D-Aspartate; SSRI: Selective Serotonin Reuptake Inhibitor

patient had specific symptoms, which have been more different as compared to the other case, after exposure to indomethacin, which were resolved with its discontinuation. It is plausible that a higher dose of indomethacin may have contributed to a more diverse and severe reaction during the hospital admission, suggesting a strong link of adverse CNS reactions with the dose. Rapid resolution of symptoms after the discontinuation of indomethacin and lack of behavioural problems gradually makes our case infallible.

Conclusion

As of 2010, 14 cases of psychosis associated with the use of indomethacin have been reported to the Committee on Safety of Medicines/Medicine Control Agency (Committee on Safety of Medicines; personal communication) [17]. There must be many medications that can cause serotonin toxicity, which are not typically included in the list of drugs known to do so and drug interactions are an important factor. The findings of multifocal clonus, agitation followed by mutism, hyperreflexia, and hypertonicity should prompt evaluation and medication review [18]. Treatment is based on severity and focuses on prompt cessation of offending agents, symptomatic treatment, and use of benzodiazepines to decrease hypertonicity and neurological excitability. We report here a case of Indomethacin Psychosis.

The effects of Indomethacin on Central Nervous System are not well known. The similarities between Serotonin and Indomethacin i.e. Indolic moiety, effects on neurotransmitters and the mechanism of action need to be studied more.

Even though a few cases have been reported, the association has not been adequately highlighted. With the widespread use of Indomethacin especially by Orthopedic Surgeons, Neurologists, Rheumatologists, patients getting delirium/psychosis might be getting misdiagnosed and it may be causing fatality.

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