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Case Report

Pharmacogenetic workup of perioperative serotonin syndrome☆

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Abstract Serotonin syndrome is gaining attention in perioperative and chronic pain settings due to the growing prevalence of multimodal therapies that increase serotonin levels and thereby heighten patient risk. A patient's genetic make-up may further increase the risk of serotonin syndrome. A case of serotonin syndrome on emergence after general anesthesia is presented. A subsequent cytochrome P4502D6 genetic test result suggested a potential alteration in metabolism. For this patient, who was taking combination antidepressant medications and receiving common perioperative medicines, additive pharmacodynamic effects converged with a pharmacogenetic predisposition, resulting in serotonin syndrome.

1. Introduction

A remarkable number of commonly used drugs and drug combinations have been associated with serotonin syndrome [1]. In both the perioperative period and chronic pain setting, the diagnosis and treatment of serotonin syndrome have gained recent attention in part due to the growing number of patients who receive multimodal therapy with such drugs [2,3]. The unresolved challenge is to correctly identify patients at risk of serotonin syndrome to the extent that perioperative and pain management may be appropriately modified with safer pharmacologic regimens. This has significant clinical impact because not only is serotonin syndrome potentially fatal, the pharmacologic interactions implicate commonly administered medications. We report on a patient who met diagnostic criteria for serotonin syndrome on emergence from general anesthesia. The novelty of this case is that a genetic test result provided potential evidence of an accentuated risk of serotonin syndrome.

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2. Case report

A 47 year old white man underwent urethroplasty for a urethral stricture. In the preoperative interview, he stated, "I wake up crazy after anesthesia." Review of his previous intraoperative records was unremarkable. Medical history was significant for remote alcohol abuse, active depression managed with duloxetine 120 mg daily, trazodone 100 mg every evening, and chronic pain treated with gabapentin 2700 mg per day.

General anesthesia was induced with fentanyl, midazolam, propofol, and succinylcholine. Anesthesia was maintained with desflurane (6% - 8% inspired; oxygen:air 50%) and vecuronium (15 mg in divided doses). Ketamine 20 mg, ondansetron 4 mg, and muscle relaxant reversal (glycopyrrolate 0.4 mg, neostigmine 2.5 mg) were administered near the end of the uneventful 8-hour procedure. During emergence, systolic blood pressure approached 200 mmHg and heart rate exceeded 160 bpm. Acceptable responsiveness to motor commands and adequate tidal volume prompted extubation.

However, autonomic hyperactivity persisted following extubation and was accompanied by whole-body muscle rigidity, with the patient's arms in an upright position (Fig. 1), trismus, tremor, confusion, agitation, ocular clonus, and complaints of pain. His temperature was 36.4° C and the tendon reflexes were not hyperreflexic. He remained in the operating room (OR). As these signs and symptoms persisted for 20 minutes after extubation, midazolam 2 mg was administered for agitation in divided doses over 5 minutes. Esmolol 50 mg in divided doses over 15 minutes was admistered for tachycardia and elevated blood pressure (BP). Intravenous (IV) fentanyl administration (two IV 50 mcg doses) for pain seemed to worsen his confusion and muscle rigidity, with no blunting of the hyperdynamic vital signs. Therefore, lorazepam 1 mg and hydromorphone 0.4 mg were administered over the ensuing hour. Given his chronic use of agents that increase serotonergic activity and untoward responses to fentanyl, serotonin syndrome was considered high on the differential diagnosis. Serotonergic drugs were held for the day. Additional causes of this presentation, including malignant hyperthermia, neuroleptic malignant syndrome, and opioid-induced muscle rigidity, were considered but thought to be less likely based on the Hunter criteria for serotonin sydrome (Table 1). Arterial blood gas analysis showed mild mixed acidosis (pH 7.26, pO_2 98 mmHg, pCO_2 49 mmHg, HCO_3 22 mmol/L). Total time in the OR after extubation was 1.5 hours.

He was transferred to the Postanesthesia Care Unit (PACU), where he received an additional 1 mg of hydromorphone in 0.2 mg doses over 25 minutes. No other medications were administered. Cyproheptadine, a serotonin antagonist, was initially considered but not administered as it is only available in the oral form and the patient was unable to cooperate. Symptoms gradually improved in the PACU over the next two hours, with normalization of his BP. With the improvement in BP, mental status, and tachycardia, he was determined fit for transfer to a general care unit. He continued to have some tachycardia while in the general care unit, with full resolution of this event approximately 24 hours after emergence from anesthesia. The patient did not recall the event.

A thorough review of previous admissions showed a nursing observation in the recovery room following a previous general anesthetic that included the use of fentanyl and ondansetron; the event was described as self-limited muscle rigidity and confusion. These occurrences prompted us to consent the patient for a saliva sample for genetic determination of the cytochrome P450 2D6 enzyme (CYP2D6), the major metabolizer of serotonergic antidepressants, including duloxetine [4]. This sample was processed in our hospital laboratory and the results were

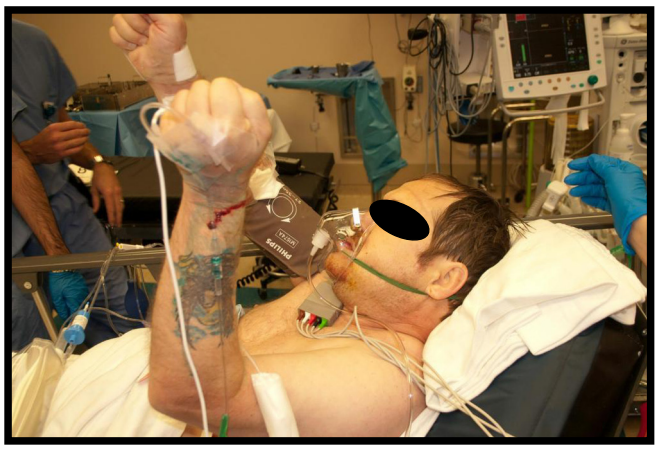

Fig. 1 Postoperative serotonin syndrome. Following the lengthy procedure and placement on the transport cart, the patient was extubated. He continued to display autonomic hyperactivity, then developed muscle rigidity, trismus, ocular clonus, and altered mental status. Fentanyl exacerbated the rigidity and confusion, while benzodiazepines, hydromorphone, and time improved the syndrome (published with the patient's permission).