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Review

Delayed emergence after anesthesia

Alexander Tzabazis MD*, Christopher Miller MD, Marc F. Dobrow MD, Karl Zheng MD, John G. Brock-Utne MD, PhD

Department of Anesthesia, Pain and Perioperative Medicine, Stanford University, Stanford, CA, USA

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Abstract In most instances, delayed emergence from anesthesia is attributed to residual anesthetic or analgesic medications. However, delayed emergence can be secondary to unusual causes and present diagnostic dilemmas. Data from clinical studies is scarce and most available published material is comprised of case reports. In this review, we summarize and discuss less common and difficult to diagnose reasons for delayed emergence and present cases from our own experience or reference published case reports/case series. The goal is to draw attention to less common reasons for delayed emergence, identify patient populations that are potentially at risk and to help anesthesiologists identifying a possible cause why their patient is slow to wake up.

1. Introduction

Delayed emergence—although in general a rare event—is a well known occurrence [1]. The low incidence complicates the design of meaningful clinical studies that could investigate potential mechanisms or clearly identify predisposing comorbidities or patient populations at risk. In addition, this low incidence also impedes the learning from personal experience. The lack of clinical studies makes it difficult to comprehend the complexity of this postoperative complication. Most published articles about delayed emergence are in the form of case reports or small case series which usually do not gain widespread distribution or attention. A potential "this could never happen to me" attitude of caregivers further facilitates negligence of this clinical problem. While we agree that there are obvious reasons for delayed emergence such as overdosing of narcotics or altered pharmacokinetics in elderly patients, most of us have had at least a few patients that were slow to wake up without any obvious reason. In this review, we want to shed light on some of the more uncommon reasons for delayed emergence. In particular we will discuss drug interactions, serotonin syndrome, postoperative delirium, central anticholinergic syndrome, psychiatric disorders, narcolepsy/sleep paralysis, surgical complications, and total spinal anesthesia.

1.1. Drug interactions

Elyassi et al [2] presented a case where a possible interaction between gabapentin and ketamine was the reason for delayed emergence. A 58-year-old man with chronic pain for cervical spinal stenosis was scheduled for cervical laminoplasty. At the end of the surgical procedure, the patient was breathing spontaneously but not responsive to

* Corresponding author at: Department of Anesthesia, Pain and Perioperative Medicine, Stanford University, 300 Pasteur Dr, Stanford, CA 94305, USA. Tel.: +1 650 736 1778; fax: +1 650 725 8052.
E-mail address: alex.tzabazis@gmail.com (A. Tzabazis).

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verbal commands or noxious stimuli. After an extensive work-up, which included magnetic resonance imaging and angiography, a definitive organic cause for the patient's state could not be established. Since the patient had received anesthesia in the past without the use of ketamine, Elyassi et al concluded that the most likely explanation for the delayed emergence in their patient was a possible gabapentin/ketamine interaction. Their patient took 900 mg of gabapentin three times per day and received a total of 100 mg of ketamine intravenously for his surgery.

Weingarten et al presented a case of a 52-year-old woman that was – after an uneventful surgery – transferred to the recovery room where she was found to be sedated but arousable. One hour after arrival in the post-anesthesia care unit (PACU), however, she became unresponsive to tactile and painful stimuli. Flumazenil and naloxone were given without any improvement. Arterial blood gas, thyroid hormones, hemoglobin, and electrolytes were within normal limits. Starting five hours after the operation and in the following 12 hours her neurological status gradually improved. She did not have any recollection of what had happened. The patient had multiple procedures done under general anesthesia in the past with only one being complicated by a similar delayed emergence. Prior to her surgery she was seen by a psychiatrist who could not find any Axis I or Axis II *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* diagnoses. Weingarten et al report that her preoperative medications included pregabalin, duloxetine, tramadol and acetaminophen/hydrocodone. In this patient a drug interaction cannot be ruled out.

The increasing age of patients undergoing surgery and their increasing complexity in terms of comorbidities and baseline medications should raise anesthesiologists' awareness of potential drug interactions in the perioperative period. One should also keep in mind that patients will not readily report the use of herbal medicine/dietary supplements unless they are specifically being asked for it. Since these substances also bear the potential for interacting with drugs given in the perioperative period [3–8] it is crucial to address this during the preoperative interview (see also section "Serotonin syndrome"). Both Valerian [4], commonly used for sleep disorders, and Kava [5], used as an herbal anxiolytic, can have sedative effects that can interfere with residual anesthetic effects in the immediate postoperative period potentially causing prolonged emergence from anesthesia. Raduege et al [5] have published an excellent article reviewing the anesthetic implications of kava medication.

1.2. Serotonin syndrome

Serotonin syndrome usually presents as a triad of neuromuscular abnormalities, autonomic hyperreactivity, and mental status changes. It usually occurs when 2 or more serotonergic agents are administered concomitantly, is typically diagnosed clinically and a high level of suspicion is warranted from clinicians. Table 1 summarizes drugs involved in the serotonin pathway. Severity of serotonin syndrome can be mild to severe. The severe form presents with muscle rigidity, hyperthermia and multi organ failure and thus shares features of malignant hyperthermia. The mild form presents usually with tachycardia, myoclonus, restlessness, dilated pupils, anxiety, and diaphoresis. Some of these symptoms are not uncommon in the immediate postoperative period and shared with other potential reasons for delayed emergence emphasizing the clinical dilemma anesthesiologist find themselves in when assessing these patients. Two diagnostic criteria are being used clinically to facilitate diagnosis of serotonin syndrome: Hunter's and Sternbach's toxicity criteria. Application in the immediate postoperative period is however limited. Wilson et al recently reviewed diagnosis and management of perioperative serotonin syndrome [10]. Rastogi et al have written an excellent review about possible opioid and serotonergic drug interactions [11] and their clinical implications.

Roy and Fortier [12] presented a case where a 41-year-old woman that had been taking venlafaxine, a serotonin norepinephrine reuptake inhibitor, exhibited profound muscle rigidity that was attributed to fentanyl but aggravated by venlafaxine. Duloxetine has been suggested as a potential risk factor for postoperative serotonin syndrome [13] as well. In this case report, a 68-year-old woman had to be re-intubated in PACU and transferred to the intensive care unit (ICU) secondary to confusion, agitation and not following verbal commands and eventually apnea. Gollapudy et al suggested that an interaction of fentanyl, which has serotonin reuptake inhibiting effects, ondansetron with its 5-HT_3 receptor blocking effects, and the co-medications of duloxetine, paroxetine, and bupropion with their selective serotonin reuptake inhibiting effects might have caused the serotonin syndrome in their patient. Fentanyl is a known to be a 5-HT_{1A} agonist, which augments serotonin release, and by weak serotonin reuptake inhibition, even further increases synaptic serotonin levels [11]. Other serotonergic opioids are tramadol, methadone, and fentanyl (Table 1). Interestingly, there is an increasing number of case reports about serotonin syndrome with concomitant use of oxycodone [14,15], which is not a phenylpiperidine opioid and should thus not interfere with serotonin reuptake [15,16]. For several reasons, such as lack of awareness among healthcare providers and also vague clinical symptoms, serotonin syndrome is difficult to diagnose in an awake patient and even more so in patients just waking up from anesthesia.

The increasing use of herbal medicine, and particular its popularity in the chronic pain population [17], might also present an easily overseen problem. St John's wort is used as an herbal anti-depressant, has been shown to inhibit serotonin, dopamine, and norepinephrine reuptake [18,19] and can thus lead to serotonin syndrome when combined with anesthetic drugs that increase serotonin release and/or further decrease its reuptake, which can present as delayed emergence [7]. Crowe and McKeating presented a case of a 21-year-old woman that received anesthesia for incision, drainage and marsupialization of a Bartholin abscess [6]. After an anesthesia that lasted approximately only 10 minutes and for which they