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Case Report

Delirium, Hyperthermia & Hypertensive Crisis after Uncomplicated Total Hip Arthroplasty in an HIV-Seropositive Patient on Highly Active Antiretroviral Therapy: A Case of Serotonin Syndrome after Meperidine Administration

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Abstract

This challenging case highlights the complex management of a 59-year old HIV-seropositive man who underwent an uncomplicated revision total hip replacement with spinal anesthesia and propofol sedation. In the PACU, the patient developed delirium, hypertension, and hyperthermia after meperidine administration that warranted medical evaluation; the patient did not sustain residual sequelae. Meperidine administration may be associated with the occurrence of serotonin syndrome and may be excabertaed in HIV+ patients on highly active antiretroviral therapeutic agents. Total joint replacements are high risk procedures in all patients, however, additional considerations are warranted in HIV+ patients who develop complications secondary to co-existing morbidities and antiretroviral regimens that may impact anesthetic care and management.

INTRODUCTION

The development and initiation of highly-active antiretroviral therapy (HAART) has led to a dramatic improvement in length of survival in patients infected with HIV. However, the utilization of HAART is associated with a wide array of drug-related side-effects, including multiple drug-drug interactions, acceleration of cardiovascular disease [1], higher incidence of myocardial infarctions, cerebrovascular accidents and metabolic syndrome [2]. HIV+ patients often require orthopedic surgical intervention due to multiple musculoskeletal pathology [3], including avascular and osteo-necrosis of the hip [4], infections of the bones and/or joints [5,6] or as a result of HIV infection and/or HAART [2].The patient consented to this case report being written, and the Institutional Review Board reviewed and approved this case report to ensure institutional compliance.

CASE DESCRIPTION

A 59-year-old man (74kg), ASA Class II with history of Human Immunodeficiency Virus infection (HIV+), hypertension, hypogonadism, osteopenia and recent bilateral hip replacement presented to the emergency department following a mechanical fall resulting in fracture of the left hip. The patient's home medications included atorvastatin, valsartan, emtricitibine/tenofovir, fosamprenavir, ritonavir, buspirone, and gabapentin. After surgical, medical and anesthetic pre-operative evaluation,

he was taken to the operating room and underwent an uncomplicated revision total hip arthroplasty under spinal anesthesia (bupivicaine), supplemental oxygen administered via simple face mask with propofol sedation (titrated to Bispectral Index Score 50-70); vital signs were stable throughout the procedure. The patient received no benzodiazepines or opioids pre-operatively or intraoperatively. The patient was taken to the post-anesthesia care unit (PACU) in stable condition at the end of the procedure and was responsive but drowsy.

Approximately thirty minutes after arriving in the PACU, the patient developed shivering, and meperidine was ordered. After administration of meperidine 12.5 milligrams intravenously, the patient became severely agitated, was unable to communicate and appeared to not understand verbal communication. Vital signs were as follows: pulse 144, blood pressure 187/102, oxygen saturation 93%, and respiratory rate 32. The patient became hyperthermic reaching a maximum temperature of 40 degrees Celsius. Supplemental oxygen (10 liters/minute) via non-rebreather face mask was initiated, and administration of lorazepam was given with no improvement in the patient's agitation or oxygenation saturation.

Differential diagnosis

Several etiologies for the acute onset of hypoxia, delirium and hemodynamic instability were considered, including the following: pulmonary embolism (including delayed fat or cement embolism), adverse drug reaction, serotonin syndrome, malignant hyperthermia, and/or cerebrovascular accident

Management

When administration of lorazepam and supplemental oxygen failed to improve the patient's mental status and vital signs, an emergent electrocardiogram (ECG) was obtained and a radial arterial catheter was placed. Arterial blood gas was significant for hypoxemia (pO_2 79 on FiO_2 60%) with normocarbia; serum chemistries were unremarkable. An esmolol infusion was initiated to control the patient's heart rate and blood pressure. An acetaminophen suppository was also given, and a cooling blanket applied for hyperthermia. A "Code Brain" was initiated as per institutional policy, and consisted of computed tomography (CT) perfusion study of the brain and neck; CT study did not reveal any identifiable evidence of stroke, hemorrhage or other intracranial abnormalities. Patient also underwent spiral CT of the chest for evaluation of pulmonary embolus, and this was also negative. Transthoracic echocardiogram was performed and was also negative for any abnormalities. The patient was evaluated by a neurologist who believed etiology for the event may have been related to medications the patient received post-operatively (i.e. meperidine).

The patient was transferred to the ICU for continued management consisting of cooling manuevers, blood pressure management with esmolol infusion. He did not require intubation, and his hemodynamics and hyperthermia improved over the next several hours without any additional treatment. His mental status improved over the course of 4-6 hours and he had no residual neurologic deficits. After one day of observation in the ICU, the patient was transferred to the rehabilitation unit and had an otherwise uncomplicated hospital course.

DISCUSSION

The case presented demonstrates a wide variety of diagnostic dilemmas and management challenges given the patient's pre-existing co-morbidities, the nature of the injury and surgical intervention, and the numerous potential complications and medication interactions. We report the first case of serotonin syndrome in an HIV (+) patient undergoing bupivicaine spinal anesthetic, propofol infusion and postoperative administration of meperidine. Serotonin syndrome typically occurs within minutes after administration of a wide variety of therapeutic agents, including but limited to meperidine. Symptoms may occur rapidly within minutes of elevated serotonin levels. Mild symptoms may consist of increased heart rate, shivering, sweating, dilated pupils, myoclonus (intermittent tremor or twitching), as well as over-responsive reflexes. Moderate syndrome signs and symptoms include additional abnormalities such as hyperactive bowel sounds, high blood pressure and hyperthermia; a temperature as high as 40 °C is common in moderate intoxication. Mental changes may include hypervigilance, insomnia and/or agitation. Severe symptoms include severe increases in heart rate and blood pressure that may lead to clinical shock. Other abnormalities in severe serotonin syndrome include metabolic acidosis, rhabdomyolysis, seizures, renal failure, and disseminated intravascular coagulation; these effects usually arising as a consequence of hyperthermia.

The incidence of post-operative delirium in patients with hip fracture and elective joint replacement has been estimated to be 21.7% and 12.1%, respectively [7]. These studies suggest that the risk for delirium is independent of pre-operative cognitive impairment as well as selection of regional or general anesthesia. This patient also had additional inherent risk factors for delirium including HIV infection and male gender [8]. However, his physiologic derangements suggested additional sources for pathology manifesting itself post-operatively.

During fixation of the femoral component of hip prosthesis, high intramedullary pressures are thought to increase the risk for fat embolus [9]. *Fat embolism syndrome* is characterized by release of fat droplets into systemic circulation after trauma to a bone, classically with the clinical triad of pulmonary distress, mental status changes, and petechial rash within 24 to 48 hours. Gurd described major and minor criteria to diagnose suspected fat embolism syndrome [9]. Our patient only met two of the three criteria, but otherwise demonstrated several similar signs and symptoms. Suspician for cerebral and pulmonary embolic events were considered and ruled out with computed tomography and echocardiography studies.

Drug interactions and adverse drug effects are often overlooked, especially when the majority of HIV (+) patients are on a multitude of medications. The wide variety of potential drug-drug interactions in HIV-seropositive patients on highly active antiretroviral therapy (HAART) poses additional considerations potentially leading to perioperative side-effects (Table 1). HIV retroviral therapy may include include non-nucleoside reverse transcriptase inhibitors (NNRTI), nucleoside transcriptase inhibitors (NRTI), and protease inhibitors (PI), entry inhibitors, and all of these agents may yield drug-drug interactions However, HIV-protease inhibitors (PIs) are known to have

Table 1: Highly Active Antiretroviral Therapy (HAART) & Common Drug-Drug Interactions.

CLASS	Common Drug-HAART Interactions	Anesthetic Specific Drug-HAART Interactions
NRTI	Prolonged effect and/or duration of NRTI with the following: Anticonvulsant: phenytoin Antifungal:ketoconazale, dapsone EtOH; alcohol H2 Blockers:cimetidine	Potential changes in clearance and duration of: Opiates: methadone
NNRTI	Prolonged effect and/or duration of NNRTI with the following: Anticoagulants - warfarin Anticonvulsants: carbamazepine, phenytoin, phenobarbital Anti-TB meds: rifampin, Herbal: St. John's wort	Prolongs $t_{1/2}$ and/or effect of: Sedatives: diazepam, midazolam, triazolam Opiates: fentanyl, meperidine, methadone
PI	Prolonged effects and/or duration of PI with the following: Anticoagulants - warfarin Anticonvulsants: carbamazepine, phenytoin, phenobarbital Antidepressants: zoloftCalcium channel blockers: nifedipine Anti-TB meds: rifampin, Herbal: St. John's wort Immunosuppressants: cyclosporine	Prolongs $t_{1/2}$ and/or effect of: Antiarhythmics: amiodarone, digoxin, quinidine Sedatives: diazepam, midazolam,triazolam Opiates: fentanyl, meperidine, methadone Local anesthetics: lidocaine
INSTI	Prolonged effect and/or duration of INSTI with the following: Proton Pump Inhibitor: Omeprazole Anti-TB meds: rifampin.	None
Entry Inhibitors	Prolonged effect and/or duration of Entry inhibitors with the following:Anticonvuslant: carbamazepime Anti-TB meds: rifampin Birth Control: oral contraceptives Proton Pump Inhibitor: Omeprazole Herbal: St. John's wort.	Potential changes in drug clearance and effect of: Sedatives: midazolam

**NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; INSTI, integrase strand transcriptase inhibitor.

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multiple drug-drug interactions due to their ability to induce or inhibit the cytochrome P3A4 (CYP3A4) pathway of hepatic metabolism [10]. Ritonavir, which this patient had been taking, is a potent CYP3A4 inhibitor, which can markedly increase the drug levels of other protease inhibitors (i.e "booster agent") [11] and several anesthetic agents, including fentanyl and midazolam [12]. Interestingly, a small study of healthy volunteers who were given ritonavir and meperidine demonstrated decreased levels of meperidine (area under the curve decreased 67%) while its metabolite normeperidine was increased (AUC increased 47%) [13]. Normeperidine accumulation can produce an excitatory syndrome including hallucination, tremor, and convulsions. Additionally, meperidine has been implicated in the precipitation of serotonin syndrome in HIV+ patients taking monoamine oxidase inhibitors or other drugs which influence serotonin transport or metabolism [14-17]. The prominent features of this syndrome include delirium, hyperthermia, hyper- or hypotension, rigidity, convulsions, coma and death.

The leading etiology for the postoperative events in this case ultimately was attributed to an untoward effect from the administration ofmeperidine. In such a case where there were multiple potential causes, both inherent to the surgery and related to the patient's co-morbidities, it is important to develop a broad and comprehensive differential diagnosis and to initiate supportive treatment while determining for the underlying cause. This patient's intraoperative anesthetic regimen consisted solely of bupivicaine spinal anesthetic with propofol infusion; therefore, the risk of intraoperative drug-drug interactions was minimal. In the post-anesthesia care unit, the only medication administered immediately prior to the development of symptoms was meperidine.

Patients with HIV present a unique challenge to the anesthesiologist not only due to their HIV-infection but also due to their complex pharmaceutical regimens which can precipitate unanticipated or idiosyncratic adverse reactions. Anesthesiologists should familiarize themselves with the wide array of HIV antiretroviral regimens. Perioperative evaluation of the HIV+ patient warrants detailed medication and social history to elicit potential sources for untoward drug interactions. A multi-disciplinary team approach is highly suggested when evaluating this patient population in the perioperative setting. In summary,

we present the first case of an HIV+ patient on HAART developing serotonin syndrome after administration of meperidine.

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