American Journal of Emergency Medicine 35 (2017) 522.e1–522.e4

Contents lists available at ScienceDirect

American Journal of Emergency Medicine

journal homepage: www.elsevier.com/locate/ajem

Case Report

Acute pulmonary edema associated with ketamine-induced hypertension during procedural sedation in the ED

Abstract

This is the case of a 58-year-old female with a history of coronary artery disease and valve replacement who was evaluated in the emergency department (ED) for a possible septic joint and underwent joint arthrocentesis under conscious sedation with ketamine. The procedure was complicated by respiratory failure secondary to hypertensive emergency with acute pulmonary edema leading to endotracheal intubation and cardiac arrest with successful resuscitation, stabilization, and subsequent improvement. This appears to be a case of a rare but significant complication caused by the potent sympathomimetic effects of ketamine previously demonstrated in a few case reports of intraoperative patients. In this report, we explore the cardiopulmonary effects of ketamine, possible predisposing factors, and pathogenesis of ketamine-induced acute pulmonary edema and discuss the clinical consequences of such a rare but serious complication of procedural sedation with ketamine.

In patients undergoing pain control and procedural sedation in the ED with ketamine, a usually transient increase in blood pressure and heart rate is often seen secondary to the drug's sympathomimetic effects [1,2]. Previously, the focus has been on ketamine's ability—as opposed to other sedating agents—to preserve cardiac output and respiratory drive [3-5]. However, as described in only a handful of case reports, mostly from perioperative patients, ketamine's profound effect on systemic blood pressure may in fact be enough to precipitate acute pulmonary edema (APE) in certain populations of patients, such as those with previous cardiac risk factors [6-8]. Malignant hypertension (HTN) is a condition in which elevated systemic blood pressure leads to damage to the cardiovascular system and/or secondary organs such as the nervous, renal, and pulmonary systems. There are many risk factors for hypertensive emergencies including prior essential HTN, coronary artery disease (CAD), drug use, preeclampsia, and renal disease. Cardiovascularly, patients may be found to be in acute myocardial infarction, acute exacerbation of congestive heart failure (CHF), and/or pulmonary edema. As observed in perioperative children and preeclamptic women, it has been proposed that the pulmonary effects of acute HTN may be due to a combination of transient diastolic dysfunction, acute transient severe mitral regurgitation [9], systemic vasoconstriction leading to increased volume return to pulmonary vasculature [10], and subsequent development of pulmonary capillary leak into alveoli secondary to increased pressures [11-13]. All of these factors likely contribute to the development of APE secondary to elevated blood pressures.

Ketamine is widely used in EDs for routine procedural sedation [14-17] with a well-recognized adverse effect at therapeutic doses of increasing sympathetic cardiac drive [18]. As such, we must better understand the possible consequences of using ketamine in patients who might not be able to tolerate medication-induced cardiac stimulation such as those with preexisting cardiac disease, like CAD [19-22]. Here, we describe a case of a patient with CAD and valve replacements who developed a hypertensive emergency with pulmonary edema after administration of ketamine for pain control and procedural sedation.

The patient is a 58-year-old female with multiple comorbidities including type 2 diabetes, HTN, CAD and coronary artery bypass grafting (CABG), aortic and pulmonary valve replacements after rheumatic fever, and gout and septic knee who presented for evaluation of wrist pain. On initial examination, the patient was afebrile, mildly hypertensive, and tachycardic but in extreme pain. Wrist and hand plain films were negative for acute pathology; routine laboratory test results were positive for leukocytosis (21.4) and mildly elevated C-reactive protein (3.785). The patient stated that this was the worst pain of her life, different from previous gouty pain, intractable and acutely worsened on the day of presentation. There was no known trauma, source of infection, or previous surgery to the wrist. On examination, the hand was mildly warm to touch, minimally swollen with diffuse tenderness over the dorsal wrist, and extreme pain with micromotion of the wrist and fingers.

The patient received cefazolin 1 g and doxycycline 100 mg for coverage of a possible septic joint and initial pain control over the first 2 hours included toradol 15 mg IV, morphine 8 mg IV, and a fentanyl bolus of 50 μg IV without satisfactory pain relief. The patient was then started on a ketamine drip at 0.15 mg kg^{-1} h^{-1} (patient's weight was 100 kg) with immediate improvement but not full resolution of pain; initial total dose of ketamine was 30 mg. Proceeding with the workup for a septic joint, the patient underwent bedside joint arthrocentesis by orthopedic with no fluid aspirated, and the patient was unable to tolerate further manipulation secondary to pain. Local anesthesia was evaluated as an approach but the patient's anatomy appeared unsuitable for a local block. After discussion of other options, risks, and benefits, the patient consented to a joint arthrocentesis under moderate conscious sedation with ketamine. The patient was placed on a cardiac monitor with nasal cannula and end-tidal carbon dioxide in place, suction and rescue intubation kit available, and 2 physicians and a nurse at bedside during the entire procedure. The initial ketamine drip was stopped; a bolus of ketamine at 1 mg/kg at 100 kg was drawn up but only 50 mg was used, given slow push over 1 to 2 minutes with achievement of moderate sedation at this dose.

The patient initially tolerated the medication well with only continued mild HTN and otherwise normal vital signs but around 12 to 15 minutes after administration of the ketamine bolus the patient was noted to be rapidly more hypertensive and tachycardic with

pressures climbing to a systolic of 230 and rates of 140 to 180 bpm. The patient simultaneously became tachypneic with intermittent mild hypoxia to 90% to 94% with no change in end-tidal carbon dioxide reading. No vomiting, choking, cyanosis, or coughing was noted and the patient was initially fully responsive and talking. However, shortly thereafter, small amounts of white frothy sputum were noted coming from her mouth; the patient's saturations slowly dropped to the mid-80s while we attempted to suction, perform airway maneuvers, and apply bag valve mask. These attempts had minimal effects on the patient's hypoxia and progression to respiratory distress. The patient was also now noted to be clamped down through her jaw with progressively worsening frothy secretions. After 5 minutes of attempts at stabilization, the decision was made to pursue rapid sequence endotracheal intubation as the patient began to have saturations in the high 70% range with cyanosis, overwhelming secretions, and respiratory failure. Direct intubation was attempted but failed after 2 attempts because of difficulty visualizing the cords secondary to copious secretions despite aggressive suctioning and atropine; intubation via glidescope was successful within 10 minutes of the first change in vital signs. Almost immediately after intubation, the patient became bradycardic despite 2 doses atropine 0.5 mg IV and went into cardiac arrest. Return of spontaneous circulation was achieved after 7 minutes of cardiopulmonary resuscitation, 3 rounds of epinephrine 1 mg IV, 2 doses sodium bicarbonate 100 mEq IV, and calcium chloride 1 g IV.

The patient's postarrest hemodynamics were within normal limits and remained stable except for persistent hypoxia, saturating 93% on the ventilator despite modification of positive end-expiratory pressure settings (started at 10), fraction of inspired oxygen 100%, and respiratory rate of 14 to 16 bpm. The patient was given 1 dose furosemide 20 mg in the ED, which she was not on at baseline. Postarrest electrocardiogram showed sinus tachycardia with persistent left bundle-branch block and ST depression on lateral leads consistent with acute ischemia as compared with previous electrocardiograms. Repeat laboratory values showed lactic acidosis (pH, 7.140; lactate, 4.6), hypercarbia (Pco_2, 59), and mildly elevated troponin (0.11). Bedside chest ultrasound, chest x-ray, and chest computed tomography all showed patterns consistent with diffuse pulmonary edema. The patient was admitted to the medical intensive care unit, continued on lasix, showed improvement of fluid status on chest radiograph and ultrasound, and was extubated 1 day later with rapid improvement in cardiopulmonary status. During the patient's hospital course, it was determined the patient had had an echocardiogram several years prior showing normal ejection fraction (EF); the echocardiogram after this event showed a reduced EF of 20% that improved to 45% by time of discharge 2 weeks later with subsequent improvement to more than 60% at time of follow-up. The patient was discharged in a stable condition back to baseline functioning with a diagnosis of flexor and extensor tenosynovitis on magnetic resonance imaging for her original complaint of wrist pain and a warning to avoid ketamine in the future.

In both adult and pediatric EDs, ketamine has become an increasingly common induction agent given its strong dissociative and analgesic effect with lack of respiratory depression, rapid onset mediated by its high lipid solubility, and distribution half-life of just 10 minutes [23,24]. These characteristics have made it a well accepted and effective medication for moderate sedation in the ED for most of our patient population [25-27]. The most common adverse effects of ketamine sedation include negative emergence phenomena, vomiting and transient HTN, and tachycardia [28-29].

Ketamine's cellular and systemic effects are not fully elucidated and are multifactorial and widespread through the body. The drug is particularly useful for procedural sedations because of its dissociative effect stemming from its action on central μ and κ receptors in the thalamolimbic system [30-32] as well as the peripheral nitric oxide/cGMP system [33]. However, it is the drug's noncompetitive antagonism of N-methyl-d-aspartate calcium channels [34] that causes the dose-dependent sympathomimetic effect [35-37] in the cardiopulmonary system responsible for the usually transient adverse effects of tachycardia and HTN as well as bronchodilation and pulmonary arteriolar vasodilation [38,39]. This hypertensive effect is seen often in patients receiving ketamine for both analgesia and sedation, in up to 25% of cases, but has not been widely recognized as possibly progressing into a hypertensive emergency. Reflective of ketamine's potent sympathomimetic effects, it has been observed in critically ill patients who are in a state of general stress-induced catecholamine depletion that use of ketamine results in an inability to compensate for the drug's profound sympathetic effect with a subsequent decrease in cardiac output and pulmonary perfusion leading to cardiac failure [40-42]. Thus, the development of hypertensive emergency induced by ketamine may be enough in certain patients with preexisting cardiac insufficiency such as CAD, valvular disease, or CHF to potentiate APE [43-45].

It is worth noting that in contrast to this proposed mechanism of sympathetically induced APE, an oft described mechanism for periprocedural APE both with and without ketamine is secondary to laryngospasm, a known but rare adverse effect of ketamine. As a form of upper airway obstruction, this mechanism causes increased negative intrathoracic pressures and, similarly to APE secondary to systemic HTN, results in increased right-sided preload, increased pulmonary capillary pressures, and subsequent alveolar fluid shift [46-48]. However, laryngospasm induced by ketamine does not appear to occur as frequently as its extreme sympathomimetic effects, [49-52] is more often observed in children [53,54] and is generally observed to be time-limited, reversed with noninvasive respiratory support and, in procedural dosing, has little risk of progression to APE [55-57], suggesting that a hypertensive emergency may promote a different mechanism for nonobstructive ketamine-induced APE. Also of note in considering ketamine's multiple effects in the cardiopulmonary system [58] is that ketamine appears to also exert an inhibitory effect on lung ENaC channels leading to decreased clearance of alveolar fluid [59] and possible contribution to APE. Thus, between sympathetically driven hypertensive emergency, increased intrapulmonary pressures, and direct intrapulmonary effects of ketamine, there appears to be a possibly distinct nonobstructive ketamine-driven cause of pulmonary edema.

Minimal research has been done on this possibility of ketamine-induced APE and only a handful of case reports suspecting its role have been published. Most of reported cases come from otherwise healthy pediatric patients undergoing elective procedures [60-63] or in chronic cocaine users with presumed pulmonary HTN [64-66]. In most of these pediatric cases, respiratory distress was preceded by tachycardia and oral frothy sputum, and lacked signs of upper airway obstruction or classic laryngospasm [67]. Gathering from the few adult case reports published, as well as animal models, it has been proposed that due to ketamine's multiple cardiopulmonary effects, use of the drug in the presence of CAD, valvular heart disease, HTN, and intrapulmonary pathology may predispose to the development of ketamine-induced APE [68-71]. One of the original case reports proposing a connection between ketamine, APE, and CAD from 1978 describes a patient with CAD who developed increased pulmonary pressures with hypoxia after administration of ketamine 1.5 mg/kg IV [72]. Other cases describe otherwise healthy patients given ketamine who develop HTN, tachycardia, and APE with frothy sputum; [73-75] one case concludes due to lack of clinical findings suggestive of upper airway obstruction or aspiration that this was a case of direct ketamine-induced APE, whereas the other describes vague “vigorous respiratory effort” they ascribe to laryngospasm. However, none of these cases are based in the ED and mostly involve much higher doses than usually used in procedural sedation in the emergency setting.

Our case describes a middle-aged woman with many of the aforementioned structural and vascular cardiac comorbidities proposed to predispose to possible complications of ketamine sedation. However, it is important to note that her cardiac history was remote; her valvular replacements had occurred as a teenager secondary to rheumatic heart disease and her CABG over 10 years prior. As per the patient, her last