Ketamine-induced QTc interval prolongation

Sir,

Ketamine is a noncompetitive antagonist of the N-methyl-D-aspartate (NMDA) receptor. It is widely used as a dissociative anesthetic and is also used as an adjunct in pain management, particularly in opioid-tolerant patients. It blocks calcium channels and depresses sodium channel function as well as having anticholinergic effects. It inhibits the re-uptake of the catecholamines and may have some nonanalgesic effects at mu and sigma opioid receptors. It is particularly useful as an anesthetic in patients with respiratory disease, as the increased catecholamines cause bronchodilation. Increased catecholamines also contribute to its stimulant effect on the cardiovascular system, where it is known to increase blood pressure and heart rate with higher doses. There have been very few reports of cardiac rhythm abnormalities related to ketamine in animal models and no human reports, specifically of ventricular arrhythmogenic effects.

Drug-induced QT interval prolongation usually occurs via alterations of intracellular ion channel function. It's associated with either prolonged depolarization due to an increase in sodium influx via sodium channels or reduced repolarization by inhibition of outward potassium channels. Potassium and magnesium abnormalities alter potassium channel function, increasing the risk of arrhythmias like QT prolongation and Torsades de Pointes.

This case will present a patient who experienced a prolonged QTc interval which was temporally associated with a sub-anesthetic infusion of ketamine, as well as discussion of available literature on potential cardiac effects of the medication.

A 21-year-old male with a history of chronic intravenous (IV) heroin use presented for a mitral valve replacement as well as aortic valve replacement. The patient had previously had his mitral valve replaced 6 months prior for valvular endocarditis. Two months following discharge from his first mitral valve repair, the patient began to use IV heroin again and subsequently developed both aortic and mitral valve endocarditis. He was admitted for repair of these valves, which was done with pericardial tissue bioprosthetic valves for both.

The patient was extubated on postoperative day (POD) #1 and his bilateral chest tubes were removed on POD #3. In addition to the patient's surgical pain, the patient had complaints of severe pain in his feet secondary to microvascular septic emboli. The acute pain service was consulted on POD #3 to help manage this patient's severe pain, which was being inadequately controlled with 30 mg morphine extended release twice a day and oxycodone-acetaminophen 5-325 1-2 tablets as needed every 4 h. The patient at this time rated the pain in his feet at 10/10 and the surgical pain at 6/10. Given the patient's history of chronic heroin use and lack of response to oral opioids, the acute pain service started the patient on a ketamine infusion to reduce opioid tolerance induced by the chronic heroin use. The patient was also started on gabapentin 300 mg tid for his peripheral neuropathic pain.

A ketamine infusion was started at 10 mg/h on the evening of POD #3. The patient's heart rhythm at the time was primarily a Mobitz type II (Wenckebach) rhythm. Earlier in the day the patient had gone into an asymptomatic accelerated junctional rhythm with rate in the 70-80 bpm range. By the time of starting the ketamine infusion, the patient was back in a Mobitz type II rhythm, with heart rate in the 60-80 bpm range. The patient's QTc prior to starting the ketamine infusion had been mostly in the 400 ms range and was 418ms by 12-lead electrocardiogram (EKG) in the morning of POD #3. Following the initiation of the ketamine infusion, the patient's QTc progressively increased overnight, based on continuous telemetry monitoring. At 0800 on POD #4, the patient's telemetry monitor was reporting a QTc of 620 ms. The patient continued ketamine infusion at this time, and by 1100 that day, the telemetry report was showing a QTc as high as 680 ms. A 12-lead EKG was obtained at that time, which showed the patient to be in a Mobitz type I rhythm and occasional premature ventricular complexes (PVC's), which had been present intermittently since his surgery. The QTc on formal 12-lead EKG was inconsistent but ranged from 580 ms to 630 ms. The acute pain service was made aware of the patient's EKG results and stopped the ketamine infusion. Following the cessation of the infusion, the patient's QTc progressively declined during the day, and by POD #5 was back to the 400-500 ms range it had been in before. During this period, laboratory tests were also done and did not reveal any electrolyte abnormalities.

During the period of starting the ketamine infusion, the only other medication change was starting the patient on gabapentin 300 mg 3 times a day, which he continued to take after the ketamine was discontinued. During the remainder of the patient's hospital admission, he continued to have primarily Mobitz type II rhythm, with occasional Mobitz type I rhythm, and infrequent PVC's. Of note, the patient had been taking metoprolol 12.5 mg twice a day and amiodarone 400 mg twice a day, which were both stopped on POD #2. The patient remained asymptomatic from his arrhythmias and was discharged on POD #7. The patient's QTc continued to remain in the 400-500 ms range until discharge.

Ketamine is commonly used as an adjunct to opioid therapy. It blocks the NMDA receptor, thereby increasing sensitivity to opioid agonists and allowing the use of lower doses, particularly in patients with a history of chronic opioid use (in this case, heroin). The sub-anesthetic doses used in this setting usually prevent the cardiovascular stimulant effects seen at higher doses. However in this case we observed a slowing of cardiac conduction to the point of QTc interval prolongation.

Prolongation of the QTc and triggering of serious arrhythmias may be a very rare event with the use of ketamine, and it is unclear if ketamine is to blame for this patient's presentation. The prior history of endocarditis, recent cardiac surgery and the stress response from surgery as well as structural alterations in the heart and conduction system due to surgery can all cause a dysfunction in the cardiac conduction pathway and lead to prolongation of the QTc. In this case though, the QTc interval was normal prior to initiation of ketamine infusion, got prolonged temporally after initiation of the ketamine infusion and then decreased back to normal after stopping the ketamine infusion. The discontinuation of prior beta-blocker therapy does complicate the scenario but the observation of resolution of the disturbance after stopping the infusion of ketamine suggests that stopping the beta blocker was probably not a major factor in the occurrence of this complication. This does not mean causation by ketamine, but it does lend the possibility that ketamine infusion can act additively and lead to cardiac conduction system dysfunction if other factors that predispose a patient to those are existent. Possibly, the presence of structural cardiac disease placed this patient at a higher risk of rhythm disturbances from the use of ketamine. Ketamine though has a long history of safe use in cardiac anesthesia, and it is a very useful adjunct in the acute pain management of the opioid tolerant patient.

We performed a PubMed literature search as well as internet sites known to evaluate and list medications reported to cause QT interval prolongation or Torsades de Pointes. Our searched words included: Ketamine, side effects, QT interval, cardiotoxicity, toxicity, intoxication, overdose, and arrhythmia. The University of Arizona Center for Education and Research on Therapeutics (www.incrediblemeds.org) has the most comprehensive database of medications that prolong the QT interval.[1] Ketamine is not on this list.

Li, *et al*. reported cardiac structural remodeling with chronic ketamine abuse in a rabbit and rat model. They concluded that ketamine may trigger ventricular myocardial apoptosis, fibrosis and increased sympathetic sprouting, leading to potential malignant arrhythmias. Interestingly, use of metoprolol prevented this.[2] In our case, the patient had not used ketamine chronically but did have structural heart disease caused by his heroin abuse and subsequent endocarditis. He was also on Metoprolol prior to his surgery which was then stopped on POD #2. Other animal studies have shown arrhythmias with ketamine in the setting of ischemic cardiac tissue.[3]

Aya *et al*. observed direct cardiac depressant effects utilizing epicardial mapping on rabbit hearts at various concentrations of ketamine. They noted a concentration-dependent lengthening of the RR interval, slowed longitudinal and transverse ventricular conduction velocity, and a prolonged ventricular refractory period without changes in ionotropic activity and also did not observe any arrhythmias.[4]

Hara, *et al.* reported that anesthetic doses of ketamine decreased influx of sodium and calcium in cardiac myocytes in a guinea pig model.[5]

In humans, a transient ST elevation (acquired Brugada EKG pattern) has been reported with ketamine intoxication (Rollin). This was thought to be related to sodium channel blockade as well.[6]

Zhao and Sun reported that ketamine inhibited both norepinephrine and serotonin transporter receptor function and also that different antidepressants modulated this inhibition differently.[7]

Koehntop *et al*. reported that ketamine increase the arrhythmogenic potential of epinephrine and the extent of enhancement was considered similar to cocaine. They also reported that successive use of intranueronal reuptake inhibitors, catechol-o-methyl transferase inhibitors, phosphodiesterase inhibitors and ketamine led to progressive increase in the arrhythmogenic potential of epinephrine.[8]

Ketamine is a useful adjunct to acute pain management of an opioid tolerant patient but does have the potential to cause cardiac rhythm disturbance in the at risk patient. We recommend use of continuous EKG monitoring for patients with significant cardiac disease so that a rhythm disturbance can be identified early in the course of its presentation which would prevent degeneration of the rhythm into a more serious disturbance.

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