Haloperidol for the Treatment of Ketamine-Induced Emergence Delirium

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Ketamine is useful, not only as a sedative, but also for its analgesic and amnestic properties as well. However, its use has been limited primarily because of its association with emergence delirium. Additional medications, such as midazolam and/or propofol, administered concomitantly with ketamine, generally reduce or eliminate this side effect. Nonetheless, severe emergence delirium can occur. We report this phenomenon, and its successful management, with haloperidol. The pharmacologic rationale for this, based upon the dopamine DA-2 receptor, is also examined. It is our recommendation that clinicians who use ketamine have haloperidol available. Haloperidol may also benefit patients with delirium occurring from illicit ketamine use.

CASE REPORT

A 20 year old female presented to the Oral and Maxillofacial Surgery clinic of University Hospital for the removal of multiple impacted third molar teeth and multiple broken down teeth with irreversible pulpitis. A total of seven decayed and impacted teeth were scheduled for removal with an estimated surgical time of approximately 60-90 minutes.

The patient's past medical history was significant for dizziness and syncope and she had a single term pregnancy. Her current medications were ibuprofen and penicillin. Furthermore, she reported no known drug allergies.

Her social history indicated a past use of marijuana. She denied other recreational drug use. However, she admitted to occasional social use of alcohol. The patient also claimed to smoke 2-3 cigarettes per day.

Physical examination demonstrated that the patient was 5'4" and weighed 160 lbs. Her lungs were clear on auscultation and her heart sounds revealed a regular rate and rhythm. Her blood pressure was 140/64 mm Hg and she had a pulse rate of 76 per minute. Furthermore, she had been NPO and her urine pregnancy test was negative.

After IV access was obtained, D5W/0.45 NS was infused. All subsequent medications were administered intravenously. Glycopyrrolate 0.2 mg was given for its antisialologue property. Following this, midazolam 5 mg was titrated to an appropriate sedative/anxiolytic effect. Next, fentanyl was administered in increments of 50 μg, 25 μg, and 25 μg. The patient required further anxiolysis and an additional dose of midazolam 2 mg was titrated. Local anaesthetics consisted of lidocaine 2% with 1:100,000 epinephrine (288 mg), mepivacaine 3% (108 mg), & articaine 4% with 1:100,000 epinephrine (72 mg). These were administered as B/L inf. alveolar nerve blocks. Local Infiltration of the anaesthetics was performed.

Because the patient remained difficult to manage, ketamine 50 mg was administered initially. Two additional doses, 25 mg each, were given over the course of the case. This anaesthesia regimen was further supplemented with propofol administered in incremental doses of 10-40 mg for a total dose of 110 mg. For the reduction of post operative swelling, 8 mg of dexamethasone was given at the beginning of the procedure. The surgery was completed in 67 minutes and the patient began to emerge from sedation. Throughout the case, and during emergence, her SaO_2 remained above 95% and her vital signs were within an acceptable normal range.

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Approximately five minutes after the completion of her surgery, the patient began to cry out loudly as well as buck and thrash in the treatment chair. She was totally unresponsive to verbal commands and had to be restrained so as not to injure herself during this violent episode. She was given O_2 via facemask and her SaO_2 remained over 95%.

After approximately 10-15 minutes, the patient's behavior did not improve, following which haloperidol 5 mg i/v was administered.

After 5 minutes, the patient began to calm down and, in another few minutes, became completely calm and quiet. No additional haloperidol was necessary. In about 10 minutes, the patient became responsive to verbal communication and she answered questions appropriately. She had absolutely no recall of her violent emergence phenomena.

The patient was then monitored for several hours. After complete recovery and assessment for street-readiness, she was discharged home in the company of her adult escort.

A phone call, later that night, verified that the patient had fully recovered without further incident. To date, no additional untoward sequelae have been reported by the patient.

DISCUSSION

Ketamine is unique in its ability to produce amnesia, analgesia, and loss of consciousness. These properties are mediated primarily through its antagonistic effect on the N-methyl-D-aspartate (NMDA) receptor. In addition, ketamine produces little, if any, respiratory depression. Ketamine is usually stable from a cardiovascular standpoint & is generally regarded as a sympathomimetic.[1] However, cardiovascular "collapse" has been reported in certain patient populations.[2, 3] Furthermore, ketamine has been reported to have a preemptive analgesic effect as well.[4, 5]

In spite of this, ketamine's use has historically been limited. This has been primarily from its association with an emergence delirium. This unpleasant side effect is generally regarded as being mediated through ketamine's agonistic effect on the dopamine DA-2 receptor.[6]

It should also be noted that ketamine is a derivative of phencyclidine (PCP) and is frequently abused as a "street" drug. Reports of patients, presenting with ketamine-induced delirium, exist within the emergency medicine literature.[7]

Clinicians, using ketamine as a sedative, have been generally successful in preventing this delirium with either concomitant midazolam, a benzodiazepine, and/or propofol, a $GABA_A$ agonist.[8, 9, 10] In addition, propofol has dopamine DA-2 receptor antagonist properties.[11, 12]

Propofol infusions have been used successfully, with ketamine, to produce excellent sedative conditions for both outpatient and office-based surgery. This "PK" technique offers significant opiate-sparing, or even opiate-free, sedative and analgesic effects. Thus, the use of opiates, and consequently opiate-associated side effects, are potentially reduced or eliminated. Furthermore, documentation of emergence delirium, occurring with the concomitant use of both propofol and ketamine, has been lacking.[9, 10]

Yet, in spite of the use of both midazolam and propofol, this particular patient suffered a profound ketamine-induced emergence delirium.

Haloperidol has been documented to have a strong antagonistic effect on the DA-2 receptor.[13] In an open double-blind study, ketamine-induced psychosis was shown to be significantly reduced with the use of haloperidol.[14] Other research supports this pharmacologic effect.[15] Typically, only low doses of haloperidol appear necessary. Specifically, an intravenous dose of 5 mg of haloperidol appears adequate in blunting the emergence delirium of ketamine.[14]

Furthermore, the pharmacologic half-life of haloperidol is significantly longer than that of ketamine. Specifically, haloperidol has a half-life of 14 to 26 hours[16] whereas ketamine has a half-life of 15 minutes for its alpha phase and 2.5 hours for its beta phase.[17]

Therefore, multiple doses or infusions of haloperidol would ordinarily not be necessary for the treatment of ketamine-induced emergence delirium. Normally, a single dose should suffice.

Haloperidol is associated with tardative dyskinesia[18] and neuroleptic malignant syndrome.[19] Haloperidol is also associated with cardiac dysrthymias.

This is especially significant in the presence of a prolonged QT interval.[20] However, these side effects occur infrequently. This is particularly notable given the relatively low dose of haloperidol which appears necessary for the treatment of ketamine-induced emergence delirium.

Thus in conclusion the clinical and "street" use of ketamine has apparently been increasing. With the concomitant administration of midazolam and/or propofol, clinicians have been taking advantage of its opiate-sparing and apparent preemptive analgesic effects. Generally, these medications have been adequate in eliminating, or significantly reducing, the emergence delirium associated with ketamine.

In spite of this, we report a patient with severe ketamine-induced emergence delirium which responded successfully to haloperidol. It is our recommendation that practitioners using ketamine have haloperidol readily available. Furthermore, haloperidol should be available for those patients who are delirious from the illicit use of ketamine.

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