An Update to Aircrew Grounding Periods After Ketamine Use

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INTRODUCTION: Ketamine is a rapidly acting general anesthetic which is globally used in surgical analgesia, as well as in the management of pain. It is also used as a recreational drug. Because of its widespread use in surgical settings, the use of this drug presents an aeromedical problem—in addition, of course, to the underlying condition for which it has been used. The literature around the mechanisms and side effects of ketamine is reasonably mature, and it is possible to make fairly dependable risk management decisions about return to flying based on the information available. Accordingly, following ketamine use it is recommended that aviators be grounded for 48 h following Aviation Medical Examiner review. If review is unavailable, the aviator should be grounded for 1 wk to allow sufficient time to identify the existence of prolonged side effects, such as psychomimetic effects or cognitive changes.

KEYWORDS: pilot, aviation, psychomimetic effects, adverse effects, aeromedical disposition.

Boyd NL, Navathe PD. *An update to aircrew grounding periods after ketamine use*. Aerosp Med Hum Perform. 2021; 92(8):670–675.

Ketamine is a rapidly acting general anesthetic that produces a state characterized by profound analgesia and anesthesia, with protected airway reflexes and skeletal muscle tone. At varying doses, it can be used as an analgesic or sedative, or for anesthetic induction or maintenance.[3,16] Ketamine is also being explored for its apparent antidepressant effects and use in other conditions such as status asthmaticus.[1,21,34] Trade names include Ketalar®.[3] Ketamine is also used as a recreational drug. Street names include Special K, Vitamin K, K, Kit Kat, Liquid E, Flatliners, Kate, Purple, and Super K.[16]

Pharmacology

Ketamine is a noncompetitive NMDA-receptor agonist. It binds to the PCP-binding site of the NMDA-receptor complex, blocking the transmembrane ion flux. NMDA receptors are found in the spinal region and thalamic, limbic, and cortical regions of the brain; therefore, ketamine influences the sensory input to the central nervous system, affecting pain and emotional responses as well as memory.[16] Ketamine has additional secondary effects on opioid receptors that helps to propagate its analgesic effect, and also affects catecholamine receptors, enhancing dopamine activity, and has an agonistic effect on alpha and beta receptors.[16,17]

Ketamine is mostly metabolized by the liver (80%), then excreted in urine and bile. The metabolite (norketamine) has weak analgesic properties with approximately 20–30% of the potency of ketamine. About 90% of a dose of ketamine is excreted in urine in 72 h, with about 2% of the dose remaining unchanged.[3,16,17]

Premedication with an anticholinergic such as atropine or hyoscine is recommended due to ketamine's side effect of hypersalivation and increased oral secretions.[2,3] Ketamine is administered by intramuscular or intravenous injection or via infusion. It can be administered intrathecally for analgesia. Oral, nasal, and rectal routes have also been described.[3]

Ketamine has two optical isomers, S-ketamine and R-ketamine. S-ketamine is more potent and, therefore, is able to be used at a lower dose for similar effects, with reduced psychoactive side effects.[33,42] However, ketamine is currently only available as a combined solution in Australia, in a racemic mixture of S-ketamine and R-ketamine. Terminal elimination half-life ranges from 100–200 min.[16]

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This manuscript was received for review in September 2020. It was accepted for publication in May 2021.

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DOI: https://doi.org/10.3357/amhp.5764.2021

Doses

For surgical anesthesia.[2,3]

- Intravenous (IV) induction: 1–4.5 mg · kg^{-1} IV (usually 2 mg · kg^{-1} provides anesthesia within 30 s of 5–10 min duration).
- Intramuscular (IM) induction: 6.5–13 mg · kg^{-1} IM (10 mg · kg^{-1} provides anesthesia within 3–4 min of 12–25 min duration.
- IV maintenance: half to full doses incrementally as required. IV Infusion: 0.5–2 mg · kg^{-1} initially, then 10–45 mcg · kg^{-1} · min^{-1}.

For procedural sedation and analgesia.[2,3]

- IV (used as a sole agent): up to 1–1.5 mg · kg^{-1} titrated to effect over 2–5 min; then half doses every 10 min as required.
- IM (used as a sole agent): 3–4 mg · kg^{-1}; then half doses every 10 min as required.

Adverse Effects

Respiratory depression. Respiratory depression is rare. Two cases have been described, one with premedication with secobarbital in a 7-yr-old patient and a second case involving ethanol.[16] Administration of ketamine is recommended to be given slowly over 60 s, as rapid administration can increase the risk of respiratory depression. Laryngospasm and other types of airway obstruction have been reported.[3]

Cardiovascular effects. Following administration of ketamine, blood pressure and pulse rate are frequently elevated; however, hypotension and bradycardia have also been reported. Arrhythmias have also been described.[3]

Other common side effects. Ketamine is associated with several side effects that usually resolve within 0.5–4 h following ketamine administration.[40] Common side effects include:

- Visual disturbances, including nystagmus and diplopia.[3,15]
- Mild gastrointestinal symptoms, including anorexia, nausea, and vomiting; however, most patients are able to tolerate liquids by mouth shortly after regaining consciousness.[3]
- Dermatological changes, including transient erythema and/or morbilliform rash.[3]

Emergence Reactions

The major limiter of the use of ketamine is the occurrence of emergence reactions. This phenomenon occurs while patients are awakening from a ketamine narcosis, experiencing hallucinations, vivid dreams, floating sensations, and delirium. This occurs more frequently in adults (30–50%) compared to children (5–15%).[16,17] Emergence reactions are often dose-dependent and may also be reduced by use of benzodiazepines such as diazepam.[15,20,38] Low doses, for example < 0.5 mg · kg^{-1}, do not typically cause major psychomimetic effects.[20]

MIMS Online advises "emergence reactions usually resolve within a few hours; however, recurrences have taken place up to 24 hours post-operatively."[3] AMH Online advises that "rarely, recurrences of emergence reactions can occur days or weeks after drug exposure."[2] Anesthetist recommendations following medical administration of ketamine requires the avoidance of driving and operating heavy machinery for 24 h postdosage.[3]

Impact of Pre-Medication Drugs on Emergence Reactions

To reduce oral secretions following ketamine administration, an anticholinergic agent is commonly administered.[2,3] Early research from 1971 into emergence reactions reported increased incidence of emergence delirium and severity of emergence reactions when atropine was delivered as a pre-medication.[5] Regardless, atropine is still commonly used as a premedication agent.[2,3,18] A prospective, randomized, double-blinded study into the effectiveness of atropine as a pre-medication for ketamine did not identify an increase in emergence reactions among the 83 pediatric patients in the study;[23] however, as described above, emergence reactions are less common in the pediatric population.[16,17]

Cognitive Disturbance

Medical short-term exposure to ketamine does not impact long-term cognitive function or personality.[16] Infrequent recreational use has also not been associated with cognitive impairment; however, repetitive recreational use has resulted in severe impairment of both short-term and long-term memory.[16,35,36] Additionally, long-term heavy users may have persisting deficits in attention and recall.[16,35,36] These effects usually resolve following cessation of chronic use.[37]

Prolonged Psychomimetic Effects

S-ketamine is responsible for the psychomimetic effects of ketamine.[16,42] The World Health Organization (WHO)[16] described a study published in 1970 by Albin et al., who performed psychometric testing for 12 mo on 221 patients following ketamine anesthesia. Test results were compared to patients who had received other anesthetics. There was no significant difference between the groups, including mental performance, hallucinations, and behavioral factors.

In contrast, a review[24] published in *Aviation, Space, and Environmental Medicine* in 1994 explored the effects of ketamine relating to prolonged psychological changes and whether use of ketamine should be considered in the context of a person's current or future occupation. The literature review identified five adult cases and three pediatric cases of prolonged psychological changes or prolonged emergence reactions over a 25-yr period. These are the same eight patients who are the only cases of prolonged psychological changes identified in a 2015 review published by WHO.[2] The details of the eight cases are outlined below.

Adult cases.[24]

1. 1971: a 29-yr-old woman, following a dose of 300 mg of ketamine for a gynecological procedure, presented at 12 mo with recurrent hallucinations. This is identified by Hersack[24]

as the only case of prolonged psychological change in their 25-yr review period. WHO proposed it was unlikely the single dose of ketamine would have caused the hallucinations and other associated symptoms at 12 mo.[16]
2. 1973: three cases of recurrent hallucinations in a group of 1400 adults were studied. Two of the three had received atropine as a premedication. Hallucinations resolved within 3 wk. Other potential causes such as recreational drugs and psychological abnormalities were reported to be ruled out. No further hallucinations were documented during the 12-mo follow-up period.
3. 1980: one case of a late occurring dream out of 60 adults studied.

Pediatric cases.[24]

1. 1976: an 11-yr-old experienced hallucinations for 5 d following ketamine dosing. They were given atropine and phenobarbital as premedications. A review at 5 mo demonstrated a resolution of psychological changes.
2. 1978: two 3-yr-olds with congenital eye abnormalities received a ketamine dose with atropine as a premedication. The children demonstrated regressive behavior (e.g., biting) and nightmares. These symptoms persisted for months but were reported to fade over time.

The following four articles reported prolonged psychomimetic effects of ketamine, but were not acknowledged by WHO or the 1994 occupational review.

An article published in 1983 reviewed psychomimetic reactions following low-dose ketamine infusion and compared 40 female patients undergoing gynecological surgery. There were 20 patients who received ketamine and were compared to 20 patients who received droperidol and fentanyl. All patients were given diazepam and atropine prior to anesthesia. At 3 mo, there were no statistically significant differences between the two groups relating to the frequency and character of dreams and nightmares. Of the ketamine group, two patients reported dreams, including one patient who reported nightmares. Hallucinatory symptoms were reported by two ketamine patients. One reported hearing whistling that they did not define as unpleasant and was not associated with fear. The other reported occasional flashbacks that were preceded by alcohol ingestion and resolved at 9 mo. Both the ketamine and droperidol group reported issues with memory and concentration at 3 mo.[29]

A case report published in 2007 reported prolonged psychomimetic effects following high doses of ketamine (3–5 $mg \cdot kg^{-1} \cdot h^{-1}$) for 6 d in the treatment of chronic regional pain syndrome in a 17-yr-old woman.[28] The patient experienced psychomimetic side effects, including agitation, anxiety, and nightmares, which were treated with midazolam and resolved within 1 mo. A conference abstract by the same author cited three cases of prolonged psychomimetic side effects from ketamine treatment of chronic regional pain syndrome; however, further details were unable to be obtained.[27]

In 2007, a study of nine patients with complex regional pain syndrome was published,[30] examining the effect of a 5-d medically induced coma from high dose ketamine infusion. Side effects included anxiety, which resolved within 2–4 wk. Two patients had mild unsettling flashbacks at 4 wk, which resolved following lorazepam administration.

In contrast, a study published in 2020 examined the side effects associated with a single dose of ketamine in treatment-resistant depression. This study revealed no significant side effects, including emergence reactions beyond 24 h following ketamine administration.[1] The 188 participants of this randomized, placebo-controlled, crossover trial were monitored for 3 mo following a 0.5 $mg \cdot kg^{-1}$ IV dose.

Discontinuation Symptoms

Discontinuation or withdrawal symptoms following regular recreational ketamine use is characterized by fatigue, reduced appetite, anxiety, dysphoria, palpitations, sweating, and shaking. Female users experience greater levels of anxiety, dysphoria, and tremors compared to male users.[10]

Ketamine and Transport Safety

Drug use can have a significant impact on the safe handling of a vehicle, which may increase crash risk.[13,14] The potential effects of a drug will vary depending on the drug class, mechanism of action, dose, and use, as well as the type of vehicle, whether by air, road, rail, or water. Most studies examining the effects of substances in the context of transport safety are focused on the effect of alcohol or commonly used drugs such as THC, benzodiazepines, and opioids.

There are limited studies examining the effect of ketamine on the safe operation of a vehicle and the majority of these are limited to road safety.[11,19,22] However, many of the skills affected by ketamine are relevant to piloting an aircraft. Acute ketamine use in healthy subjects has been identified as interfering with working memory, information processing, sustained and divided attention, general motor and executive impairment, increased reaction times, impairment of eye movements, and altered perception of the environment and time.[19] Direct observation road simulator studies have demonstrated a dose and time-related effect on driving skills, confirming that ketamine is incompatible with safe operation of a vehicle.[22]

The impact of ketamine on transport safety is difficult to quantify due to the limited fidelity of toxicological findings. Drug testing may not be performed in minor crashes and random roadside drug testing may not be representative of the population.[25] An Australian study published in 2011 identified 1.5% of drivers randomly tested at the roadside were positive for ketamine[12] and ketamine has been identified in 3.4% of fatal road accidents in Australia; however, ketamine used in medical treatment following the crash may contribute to this data.[39] Ketamine has also been detected in pilots of fatal aviation accidents; however, only two instances were detected in civil aviation between 1991 and 2005 in the United States.[4,7,9]

In considering transport accidents, the presence of recreational or prescription drugs does not necessitate causation.

The presence of drugs may have limited or no influence on the cause of an adverse event.[31,32] However, the use of medications, both prescription and recreational, remains an ongoing issue in aviation. Persistent use of nondeclared medications by aircrew have been well documented[6,8,31] and reduction of nondisclosure is likely to contribute to an improvement in aviation safety.

Aeromedical Concerns

The issue of any medication use must be considered in two contexts: 1) when used as a therapeutic agent; and 2) when used as a recreational substance.

Therapeutic setting. In making decisions about pharmacotherapy and flight safety, the Manual of Civil Aviation Medicine[26] says:

14.2.1. In considering whether a licence holder should continue to exercise licence privileges while on pharmacotherapy, certain questions should be asked:

a) Is the disease process for which pharmacotherapy is necessary in itself normally disqualifying?
b) What are the usual and expected pharmacological actions of the pharmacon in question, are they likely to endanger flight safety and, if so, what is the duration of these effects?
c) What are the possible side effects and their duration, where "side effects" refers to undesired responses to medication?

Most instances where analgesia, sedation, or anesthetic is used, at least a short-term period of grounding is required. When attempting to determine when it is appropriate to return the aviator to flying duties, one must consider both the underlying condition being treated and the potential short- and long-term effects of any medication used to treat that condition.

Ketamine is a rapid-onset anesthetic that has a multitude of uses depending on the dose administered. Most side effects resolve within 24 h from administration; however, there have been occasional reports of prolonged psychological changes beyond this time frame, specifically prolonged psychomimetic effects, such as persistent hallucinations and recurrent dreams.

Five cases in adults and three cases in children were identified in the literature over a 50-yr period of ketamine use; however, these were all reported between 1971 and 1980. Additional incidences were identified more recently, but these were predominantly associated with high doses or other contributing factors. Cases of prolonged psychomimetic effects are predominantly isolated to the first 10–15 yr of research, which potentially may be due to a shift in the research focus away from ketamine side effects, or due to a genuine reduction in cases of prolonged psychomimetic changes. Contemporary research into ketamine use is predominantly focused on either the side effects and experience of recreational use, or on exploring the potential benefits as an antidepressant using low doses.

Short-term effects include emergence reactions, visual disturbances, gastrointestinal, respiratory, and cardiovascular effects. These largely resolve within 4 h following administration of ketamine. Following a single dose or infrequent medical administration of ketamine, most adverse effects such as emergence reactions and impacts to cognition are associated with the anesthetic and emergence period. The half-life for ketamine is 2–3.5 h and, as such, these adverse effects should resolve during the procedure recovery period and are, therefore, not a major concern from an aeromedical perspective unless they persist.

The primary aeromedical concern is prolonged psychomimetic effects such anxiety, flashbacks, hallucinations, and nightmares. These effects were reported early in the literature, but the instances are few in comparison to the number of patients who have received ketamine in the past 50 yr. This literature review identified 14 adult cases since 1970, 5 of which were related to prolonged (>5 d) use of high-dose ketamine.

Historically, policy relating to the use of ketamine by military aviators required a grounding period of 3 wk in a variety of countries. However, recent reviews have reduced the grounding period to 48 h. Some militaries require review with an Aviation Medical Officer or Flight Surgeon prior to return to aircrew duties.

The ICAO Manual gives guidance about how a grounding period should be considered in aeromedical decisions:

> 14.4.5. As is the case with all pharmacotherapy, the medical examiner must always be aware of idiosyncrasy and be certain the licence holder tolerates the medicine before resuming aviation activities during such usage.

While there is strong evidence of psychomimetic effects and cognitive changes associated with chronic recreational ketamine use, single or infrequent doses received by an aviator for medical purposes are unlikely to have long-standing effects. Accordingly, unless there is a background issue of the use of ketamine in a recreational setting, it would be unlikely for single therapeutic doses to create any lasting aeromedical impacts in either the military or the civil aviation populations.

Use as a recreational substance. Ketamine is now used in various parts of the world as a recreational substance.[41] The ICAO Manual says, in its section on illicit drugs:

> 14.6.7. Other agents are also used to alter the mental state, and all produce effects incompatible with flying. It is not only the drug effects per se that are of concern, but also the psychological factors that would lead an individual to use them. It is difficult to have confidence in a pilot who uses such agents, even if he presumably has completely metabolized a given dosage. In addition, the risk of "flashback" is always present in anyone using hallucinogens.

This paper has already covered issues about pharmacokinetics, effects on body systems, and side effects. Consideration of the psychological issues around recreation use are beyond the scope of this paper, but all aeromedical decision makers must consider those factors in making a decision about the resumption of aviation duties of aircrew.

Recommendations

If the context of the ketamine use is recreational, the issue should be managed like other such substances, and any aeromedical decision must be based more on the biopsychosocial circumstances leading to the use, rather than the pharmacokinetics and side effect profile of ketamine. When defining the grounding period following administration of ketamine, the Aviation Medical Examiner should consider both the medical condition and the relevant grounding period for the medications used.

Following racemic ketamine use, a grounding period of 48 h with Aviation Medical Examiner review is recommended to permit safe return to flight or controlling. If review with an Aviation Medical Examiner is not available, then a minimum of a 1-wk grounding period is recommended to allow the aviator sufficient time to identify the existence of prolonged side effects, such as psychomimetic effects or cognitive changes. If R-ketamine (Arketamine) is used, the aviator may return themselves to aviation duties after 48 h. As with all medications, if the aviator experiences side effects, they should identify these with their Aviation Medical Examiner for further monitoring and they should remain grounded until resolution of the effects.

ACKNOWLEDGMENTS

Financial Disclosure Statement: The authors have no competing interests to declare.

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