Ketamine Revisited: Are There Any Absolute Contraindications?

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Introduction

Ketamine is one of veterinary medicine's most critically important drugs. Its utility for sedation, anesthesia, and analgesia has been long recognized in both general and specialty practice. As with all drugs, our understanding of ketamine and its optimal use continues to evolve. There is growing evidence that ketamine can be included in part of a thoughtful treatment plan for patients where it previously may have been considered risky. This emerging body of evidence invites us to revisit long-standing beliefs about when ketamine is "safe."

Physiology and Clinical Use

Significant progress has been made in understanding mechanisms of unconsciousness; however, questions persist about how anesthetics ultimately "work"[1]. Ketamine's effects are attributed to inhibition of glutamatergic signaling via antagonism of the N-methyl-D-aspartate (NMDA) receptor, although this is just one of many mechanisms of action[2]. Certainly our understanding of ketamine's molecular pharmacology is far from complete.

Clinically, ketamine has effects which are desirable in many situations. Relative to other induction agents such as propofol and alfaxalone, ketamine preserves respiratory drive and laryngeal reflexes, thus reducing the risk of apnea, hypoxemia, and aspiration; it can also promote bronchodilation in some cases. Ketamine is also a powerful and unique analgesic whereas propofol, etomidate, and alfaxalone have no analgesic properties. Hemodynamically, ketamine acts as a sympathomimetic and can promote stability through an increase in heart rate and blood pressure; this can ameliorate the bradycardia and hypotension associated with anesthetic agents. This is in contrast to propofol, which despite its own merits, invariably causes dose-dependent hypotension. Ketamine can be administered through almost any route lending to its versatility in situations where intravenous access is not straightforward, such as fractious animals or wildlife. Additionally, ketamine is a "dissociative" anesthetic, causing fragmentation of the conscious experience, not total abolishment of it. This makes ketamine especially useful for animals that may

otherwise be difficult to control, providing restraint, amnesia, and analgesia without the downsides of excessive depth.

Intracranial Pressure (ICP)

Historical wisdom states that ketamine increases ICP. As a result, ketamine has been considered contraindicated for patients with possible intracranial disease, such as encephalitis or neoplasia. The basis for this attitude stems from a series of papers from the 1970s where direct measurement of ICP in humans undergoing ketamine-facilitated procedures demonstrated an increase in ICP[3,4,5]. Recent work with traumatic[6,7] and non-traumatic[8] brain disease has challenged this attitude, arguing that ketamine does not increase ICP, especially when multiple drugs and mechanical ventilation are employed; ketamine may even decrease ICP in some cases. Furthermore, no studies have documented a link between ketamine and negative clinical outcomes linked to increased ICP. For patients in which there is concern for elevated ICP, ketamine may still be appropriate, especially if the patient has other comorbidities that make it less ideal to use agents like propofol or alfaxalone, or if a painful procedure is being undergone. Additionally, for patients with truly elevated ICP, adequate mean arterial pressure (MAP) is critical to maintain cerebral perfusion; ketamine may be beneficial in these scenarios, as it can support cardiac output.

Seizure Disorders

Ketamine has classically been believed to be epileptogenic, and this fuels fear of using ketamine in patients with a known seizure history. However, the 2023 ACVIM Consensus Statement on the management of status epilepticus recommends ketamine as a third line *anti*-epileptic agent[9]. It has been recently argued that there is no sound reason to withhold the benefits of ketamine from human epileptics; however, combination with a benzodiazepine or propofol may enhance safety[10]. Overall, the historically entrenched idea that ketamine is epileptogenic has been largely overturned, and this is particularly true in emergency management of the actively seizing patient. Ketamine is now routinely administered (per the 2023 guidelines mentioned above) to dogs presenting with seizures refractory to benzodiazepines and maintenance antiepileptics.

Ophthalmic Disease and Intraocular Pressure (IOP)

Ketamine is generally thought to increase IOP in small animal patients, and thus is sometimes avoided for ophthalmic procedures or for patients with underlying ocular disease. This concern, similar to ICP, stems from early studies in humans with significant limitations[11,12]. Indeed, multiple studies have documented that ketamine has the potential to cause a clinically relevant increase in IOP in dogs; notably, these effects can be blunted when multiple medications are used for anesthesia[13,14]. However, a recent paper demonstrated that propofol induction caused comparable increases in IOP in healthy dogs when compared to ketamine-diazepam inductions[15]. Additionally, a 2023 paper compared inductions with propofol, alfaxalone, and ketamine (each with midazolam) in cats; IOP was actually increased relative to baseline in the propofol group, but not the ketamine or alfaxalone groups[16].

In cases where acute elevations in IOP would be detrimental (e.g. underlying glaucoma, corneal surgery, phacoemulsification), ketamine should be used with caution. Ketamine can be considered for patients undergoing ophthalmic procedures where modest increases in IOP (if they occur) would be clinically irrelevant, such as non-glaucomatous enucleation (or second eye glaucomatous enucleation) or periocular/eyelid surgery.

Cardiovascular Disease and Arrhythmogenesis

One of the advantages of ketamine is it supports hemodynamic stability and can even increase cardiac output in some cases; however, some conditions, particularly arrhythmogenic heart disease and hypertrophic cardiomyopathy (HCM), are often cited as reasons to avoid ketamine. First, it is important to note that there is a wide spectrum of heart disease; many dogs with mitral valve degeneration, for example, will never experience any relevant sequelae such as left atrial dilation. Therefore, the suitability of ketamine depends mightily on the type and severity of the underlying cardiac disease. For patients where tachycardia or increased sympathetic tone would be undesirable, such as cats with HCM or animals with a known tachyarrhythmia, caution is advisable. Similarly, caution is advisable for patients with arrhythmias secondary to systemic disease, such as hemoabdomen. However, in many cases, ketamine can be incorporated at judicious doses for patients with some cardiac diseases.

Conclusion

When considering ketamine, three bedrock principles of pharmacology and anesthesia are essential.

1. No drug is benign.
2. Sola dosis facit venenum - only the dose makes the toxin.
3. There is no “safe” anesthesia or “safe” drug – only safe anesthetists.

Ketamine is a powerful, versatile, and reliable medication, but it is not without its limitations. It is irreversible, it is a controlled substance, and our understanding of ketamine is incomplete. However, the key is that all drugs have their advantages and disadvantages. Discussed above are some clinical situations where ketamine might be used with caution, but in reality, ketamine, like every drug, should always be used with some degree of caution. No medication should be prescribed with impunity. Anesthesia is a balance, and refining how we incorporate ketamine into this balance will help us continue to improve patient care.

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