Ketamine—A Narrative Review of Its Uses in Medicine

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One of the most fascinating drugs in the anesthesiologist’s armament is ketamine, an N-methyl-D-aspartate receptor antagonist with a myriad of uses. The drug is a dissociative anesthetic and has been used more often as an analgesic in numerous hospital units, outpatient pain clinics, and in the prehospital realm. It has been used to treat postoperative pain, chronic pain, complex regional pain syndrome, phantom limb pain, and other neuropathic conditions requiring analgesia. Research has also demonstrated its efficacy as an adjunct in psychotherapy, as a treatment for both depression and posttraumatic stress disorder, as a procedural sedative, and as a treatment for respiratory and neurologic conditions. Ketamine is not without its adverse effects, some of which can be mitigated with certain efforts. Such effects make it necessary for the clinician to use the drug only in situations where it will provide the greatest benefit with the fewest adverse effects. To the best of our knowledge, none of the reviews regarding ketamine have taken a comprehensive look at the drug’s uses in all territories of medicine. This review will serve to touch on its chemical data, pharmacokinetics and pharmacodynamics, medical uses, and adverse effects while focusing specifically on the drugs usage in anesthesia and analgesia.

Keywords: ketamine, analgesia, anesthesia, postoperative pain, NMDA antagonists

INTRODUCTION

One of the most fascinating drugs in the anesthesiologist’s armament is ketamine, an N-methyl-D-aspartate (NMDA) receptor antagonist with a myriad of uses. The drug, which was first synthesized in 1962 and FDA-approved in 1970, fell out of favor for a period of time, partly because of the often feared psychotomimetic effects, emergence agitation, and reputation for being a drug of abuse. However, it has recently made a resurgence across many fields of medicine. The drug is a dissociative anesthetic and has been used more often as an analgesic in numerous hospital units, outpatient pain clinics, and in the prehospital realm. It has been used to treat postoperative pain, chronic pain, complex regional pain syndrome (CRPS), phantom limb pain (PLP), and other neuropathic conditions requiring analgesia. Research has also demonstrated its efficacy as an adjunct in psychotherapy, as a treatment for both depression and posttraumatic stress disorder (PTSD), as a procedural sedative, and as a treatment for respiratory and neurologic conditions. The drug’s low cost and large therapeutic window make it an attractive agent.

Recently, celebrating its fiftieth anniversary, ketamine has a long track record as a safe and effective drug. It shares a primary mechanism of action with its slightly older cousin, fellow NMDA receptor antagonist, phencyclidine. Ketamine also has many direct and indirect interactions with other receptors in the body, perhaps explaining some of its efficacy in nonanesthetic realms of medicine. At the NMDA receptor, ketamine serves as a noncompetitive antagonist and an allosteric modifier. Because of its interaction with NMDA receptors in the brain (and perhaps with those in the periphery), ketamine, as well as other NMDA receptor antagonists, has novel utility in the prevention of hyperalgesia and
central sensitization.\textsuperscript{5} It often allows practitioners to use less opioids in the postoperative period; opioid-induced hyperalgesia and other undesirable opioid side effects can be minimized.\textsuperscript{6}

There are a number of high-quality systematic reviews in the literature describing ketamine’s use in particular fields of medicine; however, no reviews take a comprehensive look at ketamine’s uses in all territories of medicine. This review will serve to touch on its chemical data, pharmacokinetics and pharmacodynamics, medical uses, and adverse effects.

CHEMICAL AND STRUCTURAL CHARACTERISTICS

A brief mention of etymology will serve to further our knowledge. “Ketamine” is a portmanteau, a combination of the words ketone and amine. Its chemical formula is $\text{C}_{13}\text{H}_{16}\text{ClNO}$, yielding a molecular mass of 237.725 g/mol. The compound is an arylcycloalkylamine composed of a chlorophenyl ring structure bound to a cyclohexanone ring. The carbon-2 atom of the cyclohexanone ring serves as a chiral center, which has important enantiomeric implications for the drug. Because of this chirality, ketamine, which was once only available as a racemic mixture (Ketalar), is now available in both its S(+) and R(−) forms. The S(+) stereoisomer has a 4-fold greater potency in analgesia than the R(−) variety and 2-fold greater than the racemic mixture. Although it has a greater affinity, S(+) ketamine has a shorter duration than its stereoisomer.\textsuperscript{7} However, it was recently demonstrated that R(−) ketamine has a greater potency and longer-lasting effects than S(+) ketamine when used to treat depression.\textsuperscript{8}

Ketamine is commercially available as a hydrochloride salt. It is freely soluble in water and methyl alcohol and is also highly lipid-soluble with excellent penetration across the blood–brain barrier. Its pKa is 7.5. Ketamine is assayed in the plasma and urine using ultra-performance liquid chromatography–electrospray ionization–tandem mass spectrometry,\textsuperscript{9} in plasma with gas chromatographic mass fragmentographic methods,\textsuperscript{10} in urine using enzyme-linked immunosorbent assay and liquid chromatography–tandem mass spectrometry,\textsuperscript{11} and from oral fluid using liquid chromatography isotope-dilution tandem mass spectrometry.\textsuperscript{12}

PHARMACODYNAMICS

Ketamine’s numerous uses in medicine can be attributed to its incredibly complex interactions within the human body. The compound’s pervasiveness in this regard has earned the title “nightmare of the pharmacologist,”\textsuperscript{13} because research continues to provide us with more information about these interactions. The primary mechanism of action of ketamine is non-competitive antagonism of the NMDA receptor.\textsuperscript{14} This receptor requires coactivation by not 1 but 2 ligands, glutamine and glycine. When the receptor is activated by both voltage and ligand binding, Na\textsuperscript{+} and Ca\textsuperscript{2+} enter the cell and K\textsuperscript{+} exits the cell, evoking an action potential. Ketamine has been shown to significantly decrease these glutamate-driven afferent discharges.\textsuperscript{15} In addition to transmitting action potentials, open NMDA receptors allow calcium ions to enter the intracellular milieu where they can act directly as second messengers for various intracellular processes.

Ketamine’s interaction with the NMDA receptor is vital in anesthesiology, because these receptors play a key role in central sensitization.\textsuperscript{16} Central sensitization is a phenomenon in which there are increases in synaptic efficiency and reductions in inhibition, both leading toward an amplification of the pain response to nociceptive stimuli. Pain is detected in larger than expected areas because more afferent neurons are recruited. The ultimate results are hyperalgesia and allodynia, incredibly undesirable effects that can significantly decrease a patient’s quality of life. These mechanisms play a role in chronic pain, as well as in persistent postoperative pain, and a pathological protracted response to nociceptive stimuli received during surgery. Ketamine has been shown to have great value in the treatment and prevention of these entities.\textsuperscript{17} The windup phenomenon is another undesirable source of pathological pain that seems to be dependent on NMDA receptors. Repetitive nociceptive stimuli are potentiated in the spinal cord before arriving at pain centers in the brain, resulting in the perception of more severe pain.\textsuperscript{5} Through its antagonism at the NMDA receptor, ketamine can play a crucial role in disrupting these mechanisms.\textsuperscript{15}

Ketamine has effectively been used in intravenous (IV) regional anesthesia, perhaps implicating its antagonism of peripheral NMDA receptors in analgesia. However, concentrations required to achieve analgesia in IV regional anesthesia were 10- to 50-fold greater than concentrations when administered systemically. This points away from the peripheral receptor blockade, thereby having a strong analgesic effect.\textsuperscript{18} It is more likely that ketamine’s interactions with NMDA receptors in the brain, particularly in the amygdala, insula, and anterior cingulate cortex, are responsible for its analgesic effects. These aforementioned regions are involved in pain sensing and affective processing of pain. Functional MRI studies show that there is a decreased connectivity in these regions when ketamine is administered.\textsuperscript{19}
As stated earlier, ketamine interacts with many other receptors in addition to the NMDA receptor. It is known that the drug has some modulatory effect on opioid receptors—ketamine’s supposed interaction with each of the opioid receptors (κ, μ, δ) has at some point been described in the literature.20 However, a 2014 study, which used specific opioid receptor-blocking agents, suggests that ketamine exerts a central antinociceptive effect through endogenous release of opioids that act on the μ and δ (but not the κ) receptors.22 This might provide supportive evidence as to why patients receiving ketamine analgesia require less opioids.

Ketamine has also demonstrated interaction with the sigma receptor.21 Formerly thought to be an opioid receptor, sigma receptors are now being investigated as a possible target for antidepressant therapy.23 Ketamine binds both σ-1 and σ-2 receptors. The functions of these receptors are poorly understood; they might serve to modulate the NMDA receptor itself.24

Other interactions that might be responsible for antidepressant and analgesic effects involve serotonin and norepinephrine. Depression and chronic pain are known to often present concurrently, and using a combinatory treatment modality often results in the greatest therapeutic value for the patient. Serotonin and norepinephrine reuptake inhibitors have shown great promise in pain control,25 and because ketamine acts to block serotonin and norepinephrine uptake, it might explain an analgesic effect. These monoamines can play a crucial role in depression,26 and blocking their uptake potentially leads to the antidepressant effects of ketamine too.

Another noteworthy observation is that ketamine profoundly inhibits muscarinic signaling.27 Although it is not easy to say if this has any effect on anesthesia and analgesia, it does perhaps explain some of ketamine’s central (eg, memory and consciousness) and peripheral (eg, decreased sympathetic tone, bronchodilation) anticholinergic effects.

Other effects of ketamine include myocardial depression,28 inhibition of arterial smooth muscle tone,29 dopamine agonism,30 and toll-like receptor 4 suppression.31

PHARMACOKINETICS

Absorption

Bioavailability is poor with oral (17%) and rectal (25%) formulations because of extensive first-pass metabolism. Intranasal administration is possible and has a bioavailability of about 50%; this is variable and depends on how much of the compound is absorbed through the nasal mucosa and how much is swallowed. Intramuscular ketamine is favored in some cases because of a 93% bioavailability, and an administration which obviates the need for vascular access.32

Distribution

Ketamine is quickly transmitted to perfusion-rich tissues, including the brain, with a volume of distribution of 2.3 L/kg.33 After epidural dosing, ketamine is distributed rapidly throughout the systemic circulation. The distribution half-life is 7–11 minutes. Only 10%–30% of ketamine is bound to plasma proteins,34 facilitating rapid diffusion across the blood–brain barrier.

Metabolism

Ketamine is metabolized predominantly by the liver, undergoing N-dealkylation through cytochrome systems to form norketamine (80%). Cytochrome P450 3A4 is the principal enzyme responsible for ketamine N-dealkylation to norketamine; CYP2B6 and CYP2C9 isoforms are also involved.35 Norketamine is an active but less potent metabolite that is eventually hydroxylated and excreted in bile and urine. Ketamine can also be directly hydroxylated.32 Because ketamine is mostly metabolized by the liver, its metabolism is dependent on liver blood flow as well as inducers and inhibitors of the cytochrome systems.

Elimination

Ketamine has an elimination half-life of 2–3 hours. Ninety percent of the drug is excreted through renal clearance; most is metabolized, but up to 4% can remain unchanged.36 Renal clearance is 12–20 mL·min⁻¹·kg⁻¹.37

MEDICAL USES

Psychiatric conditions

As stated above, ketamine’s main effect is the antagonism of NMDA receptors, which are dependent on glutamate for synaptic transmission. The glutamatergic synaptic transmission system has been implicated as a target in the pathophysiology of depression.38 In addition to the blockage of glutamatergic mechanisms, it has been shown that activation of the alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor is necessary to achieve the antidepressant effects of ketamine, because the antidepressive effects are abolished when alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors were antagonized by 2,3-dihydroxy-6-nitro-7-sulfamoyl-benzo[f]quinoxaline-2,3-dione.39 Ketamine also has been shown to increase synthesis of brain-derived neurotrophic factor, another key factor in its

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antidepressant profile. When synthesis of brain-derived neurotrophic factor was blocked by anisomycin, the antidepressant qualities of ketamine were abolished. Regardless of the particular mechanism, many studies have shown that ketamine can be used as an effective antidepressant that has fast-acting mood-improving effects beginning on the day of administration. These effects occur on the order of hours as opposed to days as is seen with the more conventional selective serotonin reuptake inhibitors. Repeated IV infusions can prolong this antidepressant effect. Single doses can provide antidepressive effects for 4–7 days, much longer than the 3-hour half-life of ketamine. A 2013 review indicates that in both treatment-resistant depression and bipolar depression, remission was achieved in two-thirds of patients, as opposed to oral agents which show a remission rate of less than 20%. A 2012 meta-analysis of ketamine’s effectiveness in treating major depressive disorder and bipolar disorder. Most of the studies reviewed involved patients who were resistant to other treatments. The authors reported a number needed to treat of 3–5 in major depressive disorder and 4–7 in bipolar disorder at 72 hours after infusion. This should be juxtaposed against a number needed to treat of 7–16 in primary care patients with (non–treatment-resistant) depression. However, given the small sample sizes of the studies in this review, this result was not significant.

Ketamine infusions have also shown amelioration of symptoms in patients suffering from PTSD. Feder et al performed a randomized controlled trial (RCT) in which patients with PTSD received a one-time infusion of either ketamine (0.5 mg/kg) or midazolam (0.045 mg/kg). After a 2-week washout period, a crossover was performed (ie, patients received the other drug). The patients showed rapid reductions in PTSD symptom severity after ketamine infusion. The drug was well tolerated and improved the comorbid depressive symptoms in patients, thereby outperforming midazolam. Seven of the 22 patients who received ketamine first did not require a second infusion of medication because their symptoms had decreased so substantially. This was true for only one of the 19 patients who received midazolam first. The dissociative effects of ketamine were very short-lived, peaking at 40 minutes and subsiding by 120 minutes after infusion.

Ketamine has successfully been used as a pharmacologic adjuvant to psychotherapy. Krupitsky et al showed that heroin addicts receiving ketamine in addition to psychotherapy had less relapse than those who had only received psychotherapy. Better results were found in patients receiving higher doses (2 mg/kg) and those who received repeated doses of ketamine instead of only one. Ketamine has shown efficacy in the treatment of refractory status asthmaticus. Its first appearance as a bronchodilator was in 1971. Like the inhaled anesthetics, ketamine’s bronchodilator properties can be exploited in the treatment of refractory status asthmaticus. A 2013 review demonstrated that in adults and children, a bolus dose of ketamine can be useful after first-line agents fail. In the 20 articles reviewed, 18 showed a favorable response with ketamine without any major adverse effects. It is speculated that ketamine was effective through a number of possible mechanisms, including blocking NMDA receptor-induced bronchospasm, reducing nitric oxide levels, decreasing the release of inflammatory mediators, and/or spasmolytic effects through vagal nerve interactions.

Seizures
A recent systematic review advocates for the consideration of ketamine in the treatment of refractory status epileptics after first- and second-line agents have failed. The authors found that ketamine was responsible for abolishing refractory status epilepticus in 56.5% of adults and 63.5% of children, with only minimal adverse events. There is insufficient evidence to draw any firm conclusions, other than the fact that more studies using ketamine in early status epilepticus are necessary.

Miscellaneous
Ketamine has antimicrobial effects. When used at increasingly high concentrations (125 up to 500 µg/mL), ketamine has an antibacterial effect against various species of Staphylococci, Streptococci, and Pseudomonas aeruginosa. However, when used as an anesthetic in humans, the concentration of ketamine in the plasma is substantially lower (2 µg/mL), calling the clinical significance of this property into question. Begec et al showed that when combined with propofol, the antimicrobial effects of ketamine can counteract the growth-supporting characteristics of propofol. These agents are often mixed together because of their ability to maintain hemodynamic balance in patients, counterbalancing one another’s hemodynamic effects.

Ketamine has also been successfully used to blunt the pain of IV injection of propofol. Ketamine at an approximate dose of 0.3 mg/kg was effective in eliminating pain during propofol injection. A 2012 meta-analysis looked at 14 studies and 684 patients to determine the antiinflammatory effects of ketamine. Six studies and 331 patients therein met the inclusion criteria. Ketamine demonstrated a significant antiinflammatory effect, reducing IL-6 levels by an average of 71 pg/mL.
Anesthesia and analgesia

Sedation

Prehospital sedation is challenging and can pose many risks. The ideal agent would provide analgesia and sedation with minimal cardiac and respiratory effects while maintaining airway protection. Ketamine, particularly as a potent analgesic, possesses some of these properties and has been used safely in this setting, particularly in patients with trauma. Dosages can be adjusted based on route of administration and desired end point of analgesia, conscious sedation, or for general induction with dosage guidelines generally citing 1–2 mg/kg for induction, half of that for conscious sedation (0.5 mg/kg), and 0.1 mg/kg for primarily analgesic effects.63

Ketamine is often used in the emergency department for procedural sedation. This agent is particularly useful in the pediatric population because of the ability to administer it intramuscularly (IM) safely and effectively with dosages as low as 2.5 mg/kg.64,65 IM ketamine seems to have an increased risk of adverse respiratory effects including laryngospasm.66 Common adverse events associated with ketamine include recovery agitation (1%–2% children, 10%–20% adults), muscular hypertonicity, and emesis (5%–15%).67

Ketamine is not a common agent used in the intensive care unit setting for sedation, but it does have value for special situations. It can be used in combination with midazolam as sedation for asthmatic patients in the intensive care unit. It may also offer a favorable hemodynamic profile and may decrease the amount of exogenous vasopressor or inotropic support required.68

Ketamine is used for induction in pediatric patients who may have cardiovascular instability or history of congenital heart disease.69 It is also given per os (5–10 mg/kg), IM (2–6 mg/kg), or intranasally to aid with separating a small child from their parents or in patients who may become combative. Benzodiazepines and antialagolges are often coadministered to decrease agitation and secretions associated with ketamine. Ketamine exposure has been linked to neural and behavioral changes, primarily in the animal model, and this is of great concern in the developing pediatric brain. The age of vulnerability, the dosage of exposure, and the duration of exposure that cause neurotoxicity still remain too vague to be determined; it is known, however, that neurotoxicity increases with higher frequency of exposure.70

Ketamine is a useful adjuvant to inadequate regional analgesia during vaginal delivery or for obstetric manipulations. In low doses (0.2–0.4 mg/kg), ketamine provides adequate analgesia without causing neonatal depression. Constant communication is required with the patient to ensure that she is awake and able to protect her airway.71

Chronic pain

Ketamine may have a role as an opiate adjunct for cancer pain, primarily of neuropathic origin, but high-quality studies are currently lacking. The latest Cochrane review,72 provided an update to the original review conducted in 2003. Although 3 new RCTs were identified, all were excluded from the final analysis. The authors concluded that evidence-based recommendations cannot be made at this time because of the lack of quality studies available. Because of the small amount of valid RCTs, researchers did perform an independent analysis on 32 case series/reports describing ketamine as a therapeutic agent for refractory cancer pain. In aggregate, a total of 246 patients were described with the various routes of administration, dosages, durations of therapy, and types of medication coadministered. Twenty-eight of the 32 reports described improved analgesia with ketamine, and 16 of 32 described dramatic relief of refractory cancer pain.72

Ketamine has primarily been studied as a treatment for chronic (nonneuropathic) pain. In the latest review of the topic in 2009,73 outside neuropathic pain, a variety of different chronic pain conditions are described. This includes whiplash-associated pain, temporomandibular joint arthralgia, atypical odontalgia, breakthrough pain, and migraine prophylaxis. The author concluded that information supporting the efficacy and tolerability of ketamine in the long-term treatment of chronic pain is extremely limited. Because of that review, there have been some studies that assess ketamine for chronic pediatric pain, treatment of chronic pancreatitis pain, and spinal cord injury (SCI) pain.74 The only RCT of this group is regarding SCI pain, assessing ketamine as an adjunct to gabapentin. When combined with gabapentin, the SCI patients reported temporary improvement of pain scores for only 2-week duration.75

Postoperative analgesia

Because of its antagonism of NMDA receptors, perhaps in addition to its other pharmacodynamic effects, ketamine is being used more and more frequently as an analgesic. Theoretically, a blockade of the NMDA receptors should interfere with central sensitization and windup phenomenon, resulting in a decreased perception of pain perioperatively, postoperatively, and chronically. Ketamine has shown great effectiveness in postoperative pain management. It affords the practitioner an opportunity to adequately control the pain of surgical patients while at the same time subjecting patients to lower quantities of opioids. This is
especially useful in patients who have become opioid-tolerant (eg, chronic pain and cancer patients), or for those who have a difficult time handling the side effects of high doses of opioids (eg, oversedation, nausea, vomiting, and constipation). Ketamine has been used as a stand-alone anesthetic in place of bupivacaine for pediatric patients undergoing cleft palate surgery. The ketamine patients experienced lower pain scores and less sleep disturbances and dysphagia. When tested against a placebo in a pediatric population, a subanesthetic dose of ketamine given during adenotonsillectomy resulted in lower postoperative pain scores and less acetaminophen requirements. The authors also looked at the often feared emergence agitation that has been attributed to ketamine. Patients in the ketamine group had significantly lower postoperative emergency agitation scores. The Cho et al meta-analysis suggests that preoperative ketamine significantly decreases pain and analgesic needs in children over the course of both 4- and 24-hour postoperative periods.

Ketamine has also proven itself in adult surgical patients. In patients undergoing microdiscectomies, groups receiving a continuous infusion (1 µg·kg⁻¹·min⁻¹) during and after surgery experienced significantly lower pain scores and less incidences of nausea and vomiting. Kim et al found similar results in spinal surgeries, using a 0.5 mg/kg bolus followed by a 2 µg·kg⁻¹·min⁻¹ infusion. The patients in this study who received ketamine required significantly less fentanyl postoperatively and did not show any increase in adverse effects.

Nesher et al examined the effectiveness of a ketamine and morphine mixture delivered through patient-controlled analgesia (PCA). When ketamine (5 mg bolus) was combined with morphine (1 mg bolus) in IV-PCA, morphine consumption was significantly lower and patients were able to discontinue PCA earlier than those who received morphine alone (1.5 mg bolus). The ketamine group of patients also experienced less postoperative nausea and vomiting.

Zakine et al reported that patients undergoing major surgeries that usually result in significant postoperative pain can benefit from a combination of a ketamine bolus plus infusion. When the infusion is continued over a protracted time course (48 hours), patients had significantly lower pain scores and less postoperative nausea and vomiting without any increase in adverse effects. Patients who received this 48-hour ketamine infusion also used significantly less morphine than those who only received an infusion for the duration of surgery.

A number of systematic reviews have also spoken to ketamine’s effectiveness in controlling postoperative pain. In the Laskowki et al review, 78% of the ketamine treatment groups required less opioids and experienced less pain after surgery. The Elia and Tramer review showed decreases in pain intensity in the first 48 hours after surgery and less postoperative pain at a 6-month follow-up in patients who had received a 0.5 mg/kg bolus and a 0.25 mg·kg⁻¹·h⁻¹ infusion during surgery. The Subramanian systematic review included 2385 patients across 37 studies and found decreased opioid requirements in 7 of 11 studies after a single bolus dose and in 6 of 11 studies after continuous infusion. Five of 8 studies showed analgesic benefits with epidural ketamine.

Despite these positive results, we are not yet ready to recommend using ketamine routinely. Other studies do not find a significant benefit in using ketamine when compared with a placebo. Larger RCTs will be necessary to find ketamine’s niche as a postoperative analgesic.

Neuropathic pain

Within the total of 29 trials identified in the Bell review, there are 10 trials that investigate ketamine for neuropathic pain. We will exclude the discussion as related to CRPS and PLP because they are discussed in other parts of this article. Of the 10 articles identified, most articles (n = 7) investigated generalized neuropathic pain. Of the 7, 2 studies regarding topical ketamine did not show any effect, whereas the remaining 5 studies used various regimens of IV or per os medication and were all found to have a positive effect. Two studies regarding central pain and 1 study regarding postherpetic neuralgia also demonstrated positive effects of ketamine.

Kvarnstrom et al tested ketamine versus both lidocaine and a placebo in a 2003 study involving 12 patients with long-lasting, trauma-induced peripheral neuropathic pain. Ketamine (0.4 mg/kg) was shown to result in a 55% reduction in the visual analog scale (VAS) pain score versus 34% for lidocaine (2.5 mg/kg) and 22% for placebo. The result for ketamine versus placebo was significant. Seven of the 12 patients reported a greater than 50% pain reduction when receiving ketamine. Unfortunately, more than half of the patients reported an unpleasant experience while receiving the ketamine infusion, despite the analgesic effect.

Gewandter et al tested the effectiveness of a 2% ketamine plus 4% amitriptyline topical cream for chemotherapy-induced peripheral neuropathy. Their cohort included 462 cancer survivors who complained of neuropathy after receiving chemotherapy. They found no significant improvement in symptoms of numbness, tingling, and/or pain in the hands and feet (P = 0.363). A 2012 double-blinded RCT performed by Mahoney et al
demonstrated similar results. Topical ketamine cream (5%) was tested versus placebo for the treatment of diabetic peripheral neuropathy of the feet. After 1 month of daily use, the patients using the ketamine cream reported no significant treatment benefits.

CRPS has remained a difficult-to-treat entity. First, described over 100 years ago, CRPS results after a brain, spinal cord, or peripheral injury. It results in a disproportionately high level of pain, hyperalgesia, and allodynia. Because central sensitization is a driving force behind the pain perceived in CRPS, it would be logical that ketamine could be of some therapeutic benefit. A 2012 systematic review looked at the efficacy and safety of ketamine in CRPS.100 One RCT showed a 27% decrease in pain scores in the recipients of IV ketamine versus 2% in the placebo group.101 A second trial102 demonstrated that ketamine patients experienced a significantly lower pain rating than placebo group after 4.2 days of continuous infusion. The nadir of the patients’ pain occurred 1 week after ketamine infusion. The third RCT found that a topical ketamine preparation given at 2 separate occasions led to decreased allodynia but had no effect on pain.103

Patil and Anitescu104 found ketamine to be of a significant benefit in patients with CRPS (and other refractory chronic pain conditions) in a 2012 retrospective review. This study contained a subset of 18 patients with CRPS. Ketamine infusions were given for a median of 38.3 minutes, at a median dose of 0.9 mg/kg. Mean VAS scores in patients receiving ketamine infusions dropped from 8.5 to 0.8. Fifty percent of patients experienced nonserious adverse events; the most cited ones were hypertension, sedation, and vomiting. Most of the other reports of ketamine as a successful treatment of CRPS are single case reports and do not offer much for establishing a treatment paradigm. Even the aforementioned studies are small in scope. A 2013 Cochrane review reports that low-quality evidence advocates for the use of IV ketamine for CRPS treatment. More RCTs will be needed to assess ketamine’s true efficacy, if any, for the treatment of this condition.

Ketamine might also have a place in the pharmacological treatment of PLP. A 2008 randomized, crossover double-blinded study looked at the treatment of PLP with calcitonin, ketamine, and their combination. Patients receiving 0.4 mg/kg of ketamine (with or without calcitonin) reported significantly lower pain when compared with those who received placebo or calcitonin alone. Pain was reduced by 50% or more in 6 of 10 patients.106 These results corroborate a previous study in which 11 of 11 patients receiving ketamine for PLP reported decreases in VAS pain scores.107 Windup pain (provoked from repeated tapping over the dysesthetic area) was also decreased.

Miscellaneous

Sickle cell vaso-occlusive crises often require large amounts of opioids for analgesia, especially because patients develop tolerance to these opioids. It could therefore be expected that ketamine might serve as an analgesic adjuvant to opioids in patients who do not experience satisfactory relief from opioids alone. Most of the evidence up to this point is based on case reports. A 2013 review demonstrates improvement in pain scores in 14 of 17 total patients across 5 studies.108 In one series, ketamine was combined with midazolam and significantly decreased morphine requirements and pain scores.109 A 2010 case series involving 5 patients with sickle cell disease reported that 2 of 5 patients received adequate relief with a low-dose ketamine infusion. One patient had ketamine alone, and the other had a ketamine and opioid combination. The third patient did not report any benefit in pain control but did require far less opioid.110

Some literature reports improvements in headaches when patients receive ketamine. An RCT involving 18 patients demonstrated a significant decrease in the severity but not duration of migraine aura after administration of 25 mg intranasal ketamine.111 This is in congruence with a previous study in which the neurologic effects of severe disabling auras resulting from familial hemiplegic migraines were reduced in 5 of 11 patients.112

ADVERSE EFFECTS

Ketamine’s use was significantly tempered because of the possible adverse effects, primarily the psychotomimetic effects, and emergence reactions. However, some studies show that ketamine actually has an opposite effect, and its usage decreases the chances of experiencing an emergence reaction in children.27,113,114 Strayer and Nelson4 reviewed 87 studies for the adverse reactions associated with ketamine when used in procedural sedation. This study concluded that 10%–20% of adults have an “adverse psychiatric event,” which could include dreams, hallucinations, and delirium, emergence or otherwise. These effects could be tempered by preinduction counseling, relaxing music, or midazolam. The improvement of emergence reactions with the administration of midazolam has been confirmed elsewhere, with midazolam cutting the incidence by more than half.115 Other psychiatric effects that have been described include positive and negative symptoms of schizophrenia, dissociation, manic symptoms, confusion, inebriation, and memory effects. These effects, although undesirable, are ephemeral; almost all
psychiatric disturbances and feelings of intoxication resolve in 1–2 hours. A 2007 study investigated the adverse effects of ketamine across 469 healthy volunteers receiving at least a single dose of the drug. The authors found that only 2% of subjects experienced adverse mental status events leading to discontinuation of the drug. At follow-up (up to 6 months after administration), no evidence of psychiatric effects was noted. A dose of 3.75–7.5 mg midazolam can be given prophylactically to reduce the incidence and severity of psychotomimetic effects. Using midazolam can prophylactically to reduce the incidence and severity of psychotomimetic effects. 

Some of the other adverse effects of ketamine administration are transient physical effects. These include lightheadedness, diplopia, headache, nausea, dizziness, and drowsiness. One of the common side effects of ketamine, which is often used to the anesthesiologist’s advantage, is that of a temporary elevation of heart rate and blood pressure. Indeed, in patients with some conditions (eg, coronary artery disease and aortic stenosis), these events should be avoided, but in other subsets of patients (eg, hypovolemic patients and trauma patients), these effects may be desirable. Ketamine can also serve as a buffer against the hypotensive and vasodilatory effects of the halogenated agents.

Neurotoxicity has been a cited concern in epidurally administered ketamine. Some authors explicitly recommend against using it epidurally, and because of the danger, the FDA has not approved the drug for epidural use. Long-term high-dose intrathecal infusion (5 mg/d over 3 weeks) showed degenerative changes in neuroanatomy at autopsy in a case report, although this ketamine contained preservatives, which may or may not have been responsible for the deleterious effects. Most of the data concerning neurotoxicity has been in high-dose animal studies. Neuronal apoptosis in the developing brain is another concern, and ketamine should be used with caution in neonates. Rhesus monkeys that received enough ketamine to maintain anesthesia for 24 hours during the first week of life performed more poorly on a battery of cognitive and memory tests than those that did not receive ketamine. These results were long-term, persisting at least until the monkeys were 3.5 years old.

High-dose ketamine has also been implicated as a cause of uropathy. This is most often seen in chronic habitual abusers but has been reported in those receiving frequent infusions for chronic and/or cancer pain. The most common symptoms seen involve the lower urinary tract and include frequency, urgency, dysuria, and hematuria. The effects are correlated temporally with the ketamine abuse and can quickly improve on cessation of the drug. More severe effects can include bladder contraction and renal damage.

Long-term ketamine use has been implicated as a causeative agent in hepato- and renal-toxicity. Animal studies have shown that high-dose ketamine administered over long periods of time can cause fatty degeneration, fibrosis, and increases in lactate dehydrogenase, as well as hydropic changes of the kidney, glomerular atresia, and proteinuria. Anesthetic doses of ketamine and low-dose continuous infusions have caused modest increases in transaminases in humans, but this has not been found at single doses under 1 mg/kg.

Some practitioners are concerned with ketamine causing an increase in intracranial pressure, but recent studies have shown that this is not the case and that ketamine might actually confer a protective (lowering) intracranial pressure when used in patients with traumatic brain injuries. Because of the psychedelic effects, ketamine is desired by some users and has become a drug of abuse. Therefore, care must be taken to prevent the drug from falling into the hands of a recreational user; proper disposal and drug-wasting measures should be exercised.

CONCLUSIONS

The present is a great time for ketamine. When we “dissociate” ketamine the clinical drug from ketamine the club drug, we are left with a powerful and incredibly versatile therapeutic agent whose potential has not yet been completely unlocked. However, despite ketamine’s 50-year tenure as a safe and effective drug, there remains much to be uncovered, both biochemically and clinically. As more finite details of the compound’s pharmacodynamics are elucidated, we will potentially discover even more therapeutic uses. Ketamine has proven itself to be an effective anesthetic, analgesic, procedural sedative, refractory respiratory treatment, and refractory antidepressant. For major surgical procedures, it has a place as a postoperative analgesic while allowing anesthesiologists to use less opioids, providing practitioners with another option for a balanced anesthetic technique. Its recent performance in depression trials casts hope on this difficult-to-treat public health problem. Like any medication, ketamine is not without its adverse effects—it undoubtedly does increase the incidence of psychotomimetic symptoms. Although these effects can be
tempered with medication and a relaxed environment, they do still exist. Because ketamine is being used more frequently in long-term repeated infusions for chronic pain, neuro-, uro-, and hepatotoxicity become more concerning and warrant more high-quality trials. The future for ketamine looks bright—as more research is performed, we will garner a deeper understanding of exactly how to implement this powerful drug into our therapies across many fields of medicine.

REFERENCES


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