Final Order No. DOH-17-1390-DS -MQA

FILED DATE AUG 07 2017
Department of Health
By: Angel Sanders
Deputy Agency Clerk

STATE OF FLORIDA
BOARD OF NURSING

IN RE: THE PETITION
FOR DECLARATORY
STATEMENT OF
AMBERLY L. PORTO, RN
_____/

AMENDED FINAL ORDER

THIS CAUSE came before the BOARD OF NURSING (hereinafter Board) pursuant to §120.565, Florida Statutes, and Rule 28-105, Florida Administrative Code, at a duly-noticed meeting in Tampa, Florida on June 8, 2017, for the purpose of considering the Petition for Declaratory Statement (attached as Exhibit A) filed by AMBERLY L. PORTO, RN (hereinafter Petitioner). Having considered the petition, the arguments submitted by counsel for Petitioner, and being otherwise fully advised in the premises, the Board makes the following findings and conclusions.

FINDINGS OF FACT

1. This petition was noticed by the Board in Vol. 43, No. 10, dated January 17, 2017 of the Florida Administrative Register .

2. Petitioner, AMBERLY L. PORTO, RN, is registered nurse licensed to practice nursing in the State of Florida, having license number RN 9270410.

3. Petitioner was licensed in 2007.

4. Petitioner earned her Bachelor's Degree in Nursing from the University of South Alabama, and is currently pursuing a Master's Degree in Nursing from the University of Tampa.

5. In 2008, Petitioner completed End-of-Life Nursing Consortium training, a 25-hour education program in pain and symptom management and other aspects of palliative care.

6. Petitioner was certified as a Medical Surgical Registered Nurse in 2013.

7. Petitioner focuses her clinical practice on adult medical surgical and palliative care for patients who qualify for in-patient palliative care at Tampa General Hospital, and has nearly 10 years experience working with palliative care patients.

8. Petitioner inquires if it is within the scope of her practice to administer 0.5 mg/kg or less of ketamine intravenously or intramuscularly for analgesia to end-stage patients receiving palliative care who suffer from pain that is chronic, intractable or difficult to control as an alternative to, or adjunct to, opioids.

9. The administration of ketamine would be pursuant to an order by a licensed physician or advanced registered nurse practitioner under policies and procedures established by an inter-disciplinary team at Tampa General Hospital.

10. The hospital pharmacy will prepare the dosage for administration.

CONCLUSIONS OF LAW

1. The Board has jurisdiction over this matter pursuant to § 120.565, Florida Statutes, and Rule 28-105, Florida Administrative Code.

2. The petition filed in this cause is in substantial compliance with the provisions of § 120.565, Florida Statutes, and Rule 28-105, Florida Administrative Code.

3. The scope of practice of a registered nurse is defined in § 464.003(20), Florida Statutes, to include:

The administration of medications and treatments as prescribed or authorized by a duly licensed practitioner authorized by the laws of this state to prescribe such medications and treatments.

WHEREFORE, the Board hereby finds that under the specific facts of the petition, as set forth above, it is within the scope of the education, training and experience of Petitioner to administer 0.5 mg/kg does of ketamine to palliative care patients for analgesic purposes.

DONE AND ORDERED this 4th day of August, 2017.

BOARD OF NURSING

Joe R. Baker, Jr.
Executive Director *for*
Jody Bryant Newman, EdD, EdS, Chair

NOTICE OF APPEAL RIGHTS

Pursuant to § 120.569, Florida Statutes, the parties are hereby notified that they may appeal this Final Order by filing one copy of a notice of appeal with the clerk of the department and by filing a filing fee and one copy of a notice of appeal with the District Court of Appeal within thirty days of the date this Final Order is filed.

CERTIFICATE OF SERVICE

I HEREBY CERTIFY that a true and correct copy of the foregoing Final Order has been furnished by U.S. Mail to Cynthia A. Mikos, Esquire, 401 East Jackson Street, Suite 3100, Tampa FL 33602, and by email to Donna Oxford, Donna.Oxford@myfloridalegal.com this 7th day of August, 2017.

Angel Sanders

Deputy Agency Clerk

TO: Adrienne C. Rodgers, Chief
Bureau of Health Care Practitioner Regulation

FROM: Joe Baker, Jr., Executive Director
Florida Board of Nursing

DATE: August 1, 2017

RE: Delegation of Authority

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During my absence this afternoon through Friday, August 4, 2017, the following managers are delegated authority for the board office:

8/1-2	Vickie Boyd	Regulatory Supervisor
8/3-4	Kathy Herron	Regulatory Supervisor

Thank you.

JBjr/ms

FLORIDA DEPARTMENT OF HEALTH
BOARD OF NURSING

Petition for Declaratory Statement
Before the Board of Nursing

In re: Amberly L. Porto, RN

_____/

Petitioner, Amberly L. Porto, RN, by and though the undersigned attorneys and pursuant to Florida Statutes §120.565 and Florida Administrative Code Rule 28-105, seeks the Florida Board of Nursing's ("Board") opinion as to whether the intravenous or intramuscular administration of low dose ketamine for purposes of analgesia in a palliative care setting is within her scope of practice as a registered nurse.

1. Petitioner, Amberly L. Porto, is a registered nurse licensed by the Florida Board of Nursing pursuant to Florida Statutes Chapter 464 holding license number RN 9270410 since 2007. She can be contacted through undersigned counsel.

2. Ms. Porto is currently employed at Tampa General Hospital ("TGH") as a Clinician in the Acute Care Division on the Complex Medicine Unit, where she has practiced since 2008.

3. After earning a Bachelor's Degree in Biology from the University of Georgia, Ms. Porto went on to graduate with honors from the University of South Alabama, earning a second Bachelor's Degree in Nursing in 2007. Ms. Porto is now working towards her Master's Degree in Nursing at the University of Tampa and she is on track to graduate in 2019.

4. In 2008, Ms. Porto completed End-of-Life Nursing Education Consortium ("ELNEC") Training, a 25-hour educational program that provides training in pain and symptom management, communication strategies, spiritual support, care at the end of life, ethics, and other

aspects of palliative care. In addition, she has been certified as a Medical Surgical Registered Nurse since 2013. A copy of Ms. Porto's curriculum vitae is attached as Exhibit 1.

5. Ms. Porto focuses her clinical practice on Adult Medical Surgical & Palliative Care, rendering patient care and assisting other nursing staff to care for patients who qualify for palliative care including those housed in the three Palliative Care Suites located in the Complex Medicine Unit. TGH's Palliative Care Suites provide a private setting with home-like comforts for patients suffering from terminal illness who require inpatient care. One of her roles includes providing direct patient care and clinically supervising other nurses in the Acute Care Division.

6. Ms. Porto seeks the Board's determination as to whether it is within her scope of practice as a registered nurse to administer 0.5 mg/kg or less of ketamine intravenously or intramuscularly for patients receiving palliative care who suffer from pain that is chronic, intractable, or difficult to control as an alternative to, or adjunct to, opioids. This administration of ketamine would be conducted pursuant to an order by a duly licensed practitioner and in accordance with policies and procedures established by TGH. At no time would Ms. Porto administer ketamine at a dose that is deemed to be general anesthesia.

7. Ketamine is approved by the United States Food and Drug Administration as a nonbarbiturate anesthetic producing an anesthetic state characterized by profound analgesia, normal pharyngeal-laryngeal reflexes, cardiovascular and respiratory stimulation, and occasionally a transient and minimal respiratory depression. Ketamine is noted for its ability to produce a state of anesthesia while preserving respiratory drive and protective airway reflexes[1].

8. In low or subdissociative doses ketamine has been shown to confer "potent, analgesic and amnestic effects that are accompanied by preservation of protective airway

[1] Rakic and Golembiewski, *Low-Dose Ketamine Infusion for Postoperative Pain Management*, 24 **Journal of PeriAnesthesia Nursing**, 254, 254 (August 2009).

responses, spontaneous respiration and cardiopulmonary stability."[2] Analgesic dosages of ketamine are generally less than 1.0 mg/kg and are commonly referred to as low dose ketamine. *Id.* In low doses, ketamine has shown opioid-sparing effects which have made it a useful agent in many situations, including for pain relief post-operatively, in palliative care settings, and for patients with a tolerance to opioids. It is especially helpful when seeking to avoid the respiratory depression associated with the use of opioids and benzodiazepines. A multitude of trials and studies have borne out the efficacy of low dose ketamine in palliative care, resulting in its widespread use in such settings. Eric E. Promrner, M.D.'s article *Ketamine for Pain: An Update of Uses in Palliative Care*, attached hereto as Exhibit 2, provides a comprehensive overview of the modern role of ketamine in palliative care.

9. In the Amended Final Order dated February 28, 2014 in *In Re Petition for Declaratory Statement of Lancia L. Simmons, RN*, this Board approved Ms. Simmons' administration of low dose ketamine in the burn unit of TGH for pain control during time limited procedures such as dressing changes. During 2003, in *In Re Linda C. Noelke, RN*, the Board concluded that it was not within Ms. Noelke's scope of practice to administer ketamine for purposes of rendering a patient insensible to pain in an ambulatory surgery center when no anesthesia provider was present. Here, Ms. Porto, like Ms. Simmons, seeks to administer low dose ketamine for pain control.

10. The administration of ketamine by registered nurses ("RNs") has come before Boards of Nursing in other states where licensees have sought regulatory guidance. The New York and Oregon Boards of Nursing have specifically addressed the issue of ketamine

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[2] Motov, Rockoff, Cohen, et al, *Intravenous Subdissociative-Dose Ketamine Versus Morphine for Analgesia in the Emergency Department: A Randomized Controlled Trial,* 66 **Annals of Emergency Medicine,** 222-229 (September 2015).

administration by RNs and have issued policy statements which state it is within the scope of practice of registered nurses to administer low dose ketamine as long as specific criteria are met. The Texas Board of Nursing has discussed the issue and while it declined to specifically issue a policy statement, it implies in its FAQs that it may be within the scope of practice for registered nurses with appropriate training and in appropriate settings to administer low dose ketamine. The State of Washington's Nursing Care Quality Assurance Commission in an Advisory Opinion dated 3-13-15 found that low-dose ketamine provides effective analgesia for the treatment of post-operative pain, neuropathic pain, and chronic pain, especially related to patients with opioid tolerance. The Washington board cited studies finding that use of ketamine results in a decrease in opioid requirements in surgical and non-surgical patients, fewer interventions to manage severe pain, a positive impact on knee immobilization after total knee arthroplasty, a decrease in post-operative nausea and vomiting and reduced pain scores for as long as one-year after surgery. They concluded that an RN may administer analgesic, sedating and anesthetic agents for acute and chronic pain using low-dose anesthetics and for emergency care, including rapid sequence intubation under certain conditions. The Minnesota Board of Nursing in its Statement of Accountability for Administration of Medications Classified as Anesthetics by the Registered Nurse adopted in October 2005 and reaffirmed in December of 2009 found that the administration of medications classified as anesthetics, such as ketamine, for the purpose of procedural sedation and analgesia require particular attention by the RN, including specialized competencies and immediate availability of emergency personnel. The Wyoming State Board of Nursing in its Opinion: IV Administration of Low-Dose Ketamine for Pain in Adults dated October 10, 2013 and revised October 2016 found that it is within the scope of practice for an appropriately trained RN to administer and monitor low-dose ketamine infusion for the purpose

of pain control. The Wyoming Opinion outlines that a ketamine infusion for pain relief should be initiated in a nursing care unit with a low patient to nurse ratio, such as the emergency department or palliative care area, by RNs with additional education, skills and demonstrated competence. The Nebraska Board of Nursing in its Advisory Opinion on Low-Dose Ketamine adopted June, 2014 and reaffirmed in April 2016 also approved the appropriately trained RN to administer and monitor low-dose ketamine infusions for pain control. Arizona, Alaska and Nevada have also issued opinions that RNs may administer low-dose ketamine for analgesia in select situations.

11. The scope of practice of a registered nurse is defined in Florida Statutes §464.003(20) as follows:

> "Practice of professional nursing" means the performance of those acts requiring substantial specialized knowledge, judgment, and nursing skill based upon applied principles of psychological, biological, physical, and social sciences which shall include, but not be limited to:
>
> (a) The observation, assessment, nursing diagnosis, planning, intervention, and evaluation of care; health teaching and counseling of the ill, injured, or infirm; and the promotion of wellness, maintenance of health, and prevention of illness of others.
>
> (b) The administration of medications and treatments as prescribed or authorized by a duly licensed practitioner authorized by the laws of this state to prescribe such medications and treatments.
>
> (c) The supervision and teaching of other personnel in the theory and performance of any of the acts described in this subsection.
>
> A professional nurse is responsible and accountable for making decisions that are based upon the individual's educational preparation and experience in nursing.

12. Ms. Porto would administer ketamine at sub-anesthetic doses as prescribed or authorized by a duly licensed practitioner authorized to prescribe it. Ms. Porto has been informed that TGH would develop policies and procedures approved by a multidisciplinary team, including representatives from pharmacy, medicine and nursing, whereby ketamine may be administered to patients receiving palliative care under conditions with which Ms. Porto would comply.

ARGUMENT

13. The Board of Nursing has discretion to determine if a particular set of facts, with respect to a specific licensee, results in actions which are within the scope of practice of the registered nurse.

14. The registered nurse may administer medication pursuant to an order of a duly authorized practitioner. In the facts presented, Ms. Porto would administer ketamine pursuant to the order of a duly authorized practitioner.

15. The registered nurse is responsible and accountable for making decisions that are based upon the individual's educational preparation and experience in nursing. Ms. Porto has nearly 10 years of experience working with palliative care patients in the Complex Medicine Unit of a large, urban hospital. She is an End-of-Life Nursing Education Consortium Palliative Resource Nurse, a Certified Medical Surgical Registered Nurse, and will demonstrate her competence to safely administer ketamine should the Board approve this petition. Under these circumstances, Ms. Porto's educational preparation and experience in nursing support her ability to administer ketamine in these limited situations.

16. Ms. Porto will administer ketamine in low doses to patients for pain relief as part of a palliative care regimen. This administration of ketamine will be accomplished pursuant to policies and procedures developed by the hospital. Ms. Porto will not administer ketamine as an anesthetic.

17. This Board and multiple other boards of nursing across the country have determined that the administration of low-dose ketamine for analgesia is within the scope of practice of a registered nurse, like Ms. Porto, under conditions like those outlined herein.

WHEREFORE, Ms. Porto respectfully requests that the Board issue a declaratory statement opining that her administration of low dose ketamine to patients receiving palliative care for analgesia is within her scope of practice as a registered nurse.

Respectfully submitted,

JOHNSON POPE BOKOR RUPPEL & BURNS, LLP
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401 E. Jackson Street, Suite 3100
Tampa, FL 33602
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CERTIFICATE OF SERVICE

I hereby certify that a true and correct copy of the fully executed foregoing instrument has been furnished via email (lee_ann_gustafson@oag.state.fl.us) and U.S. Mail to LeeAnn Gustafson, Office of the Attorney General, The Capitol, PL-01, Tallahassee, FL 32399 and via facsimile (850-

487-9537) and U.S. Mail to the Florida Department of Health, Agency Clerk, 4052 Bald Cypress Way, Bin A02, Tallahassee, FL 32399 on this 11th day of January, 2017.

Cynthia A. Mikos

PORTO, AMBERLY

15413 Fire Rock Place, Ruskin, FL 33573 | (W) 813.844.3946 (C) 706.372.0031 | aporto@tgh.org

EDUCATION

University of South Alabama, Mobile, Alabama
Bachelors of Science, Nursing
Cum Laude
2007

University of Georgia, Athens, Georgia
Bachelors of Science, Biology

University of Tampa, Tampa, Florida
Masters of Science, Nursing **2002**
Area of Concentration: Family Nurse Practitioner
Expected Graduation: 2019 **2016-Present**

EXPERIENCE

Tampa General Hospital, Tampa, Florida
Complex Medicine Unit, 2008-Present
Busy 65 bed medical/surgical telemetry unit in a level 1 trauma center and teaching hospital. Dedicated floor for The University of South Florida Internal Medicine. Direct patient care with diverse populations of patients including HIV/AIDS, palliative care, peritoneal dialysis, and ventilator dependent patients.
Clinical Area of Focus: Adult Medical Surgical & Palliative Care

Clinician

Duties include: **2012 – Present**

- Supervise 120 staff members consisting of registered nurses, patient care technicians, unit coordinators, and cardiac monitor technicians
- Yearly evaluations for all staff members
- Schedule for all staff
- Discipline staff
- Chart audits
- Monitoring compliance of unit for Joint Commission, OSHA, and AHCA standards
- Follow-up of patient and family complaints or concerns
- Staff education
- Chart/case reviews
- Completion of Root Cause Analysis related to wounds, infections, and falls
- Interview and hiring of applicants
- Charge Nurse
- Staff Nurse

Interim Nurse Manager

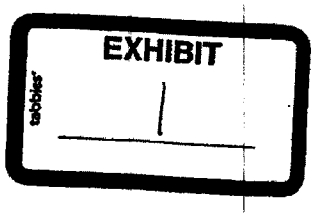
Clinical Nurse/Charge Nurse **March 2016 – August 2017**

Acute Care Rotation Nurse **2008-2012**

2007

LICENSURE AND CERTIFICATION

2007-present	Registered Nurse	FL Licensure No. RN 9270410
2005-present	BLS Certification	
2008-present	End-of-Life Nursing Education Consortium Palliative Care Resource Nurse	
2013-present	Certified Medical Surgical Registered Nurse	



JOURNAL OF PALLIATIVE MEDICINE
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Ketamine for Pain: An Update of Uses in Palliative Care

Eric E. Prommer, M.D.

Abstract

Ketamine is a lipophilic, general anesthetic. When given at subanesthetic doses, it also has been found to be an effective analgesic, with efficacy in cancer-associated neuropathic pain, ischemic pain, and regional pain syndromes. It can be administered orally, intravenously, subcutaneously, and topically, and interacts with several receptors important in pain management, most importantly the N-methyl-D aspartate (NMDA) receptor. Blockade of the NMDA receptor is associated with reversal of opioid tolerance. Ketamine is metabolized via cytochrome P450 3A4, although no significant interactions have been reported. Ketamine is considered one of the World Health Organization (WHO) essential drugs for the management of refractory pain.

Introduction

PAIN IS A COMMON EXPERIENCE for patients in the palliative care population. The World Health Organization(WHO) analgesic ladder is a useful concept for the management of pain, with its use leading to successful analgesia approximately 90% of the time.[1] In the context of opioid use, the concept of opioid responsiveness becomes important. Opioid responsiveness can be defined by "degree of analgesia achieved as the dose is titrated to an endpoint defined either by intolerable side effects or the occurrenceof acceptable analgesia."[2] In cases where opioid responsiveness becomes an issue, other modalities must be considered. One of the most important causes of decreasing opioid responsiveness is N-methyl-D-aspartate(NMDA) overactivity.[2] The use of NMDA antagonists is advocated as a way of improving analgesia when poor opioid responsiveness is identified.[2] Ketamine, a potent NMDA antagonist, was developed in 1962[3] as an anesthetic agent, and has been shown to have minimal effect on the cardiovascular system or respiratory systems.[4] In 1990 the first reports of subanesthetic uses of ketamine were described for cancer pain, with low doses showing efficacy for opioid-resistant pain.[5] The purpose of this article is to review the pharmacodynamics, pharmacology, drug interactions, and clinical uses of ketamine for pain. Methods of administration and management of adverse effects will also be highlighted.

Structure/Chemistry

Ketamine is a phencyclidine (PCP) derivative.[6] (Figure 1). Ketamine contains a chiral structure at the carbon # 2 position, allowing the formation of two isomers. In the United States, ketamine is available as a racemic mixture that contains equal amounts of the two isomers S (+) and R (-) forms. The S (+) enantiomer is available in Europe. Ketamine is a highly lipophilic and water-soluble general anesthetic with a molecular weight of 274.[3] It is highly lipophilic (lipid solubility 5 to 10 times that of thiopental) and easily crosses the blood-brain barrier.[7]

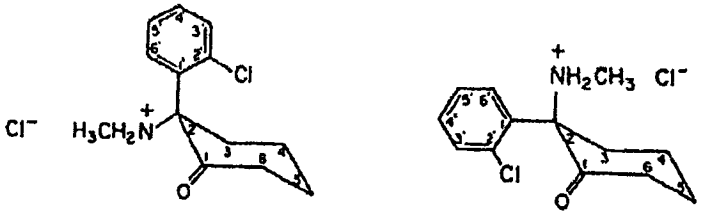
NMDA receptor and chronic pain

Excitatory synaptic transmission in the central nervous system is mediated by amino acids, most notable of which is glutamate.[8] Amino acids bind to either ionotropic (ionic channels) or metabotropic (G coupled) receptors.[9] The three chief ionotropic receptors are the NMDA, alpha amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), and kainate receptors.[9] The NMDA receptor is a transmembrane protein that acts as an ion channel for Na^+, Ca^{++}, and K^+ ions, influencing neuronal excitability. NMDA is a heterodimer consisting of two subunits.[10] Located throughout the nervous system, NMDA receptors mirror opioid receptors in location.[10] At resting state the channel is inactive due to Mg^{++} blockade. When activated, the Mg^{++} ions are released out of the channel and then Ca^{++}, Na^+, and K^+ ions enter.[11] Ca^{++} influx is important for many of the intracellular processes that contribute to chronic pain states. Calcium influx, through an activated NMDA receptor, activates second-messenger systems, leading to a neuronal state of "hyperactivity" commonly seen in chronic pain.[12] NMDA activation is responsible for neuronal hyperexcitability, which is clinically manifest as persistent hyperalgesia, spontaneous pain, allodynia, and radiation of pain.[12]

Molecular changes due to Ca^{++} influx

It is well established that activation of the NMDA receptor initiates intracellular processes that lead to problems with neuronal hyperexcitability.[13] Excitatory amino acids (EAA),

Division of Hematology/Oncology, Mayo Clinic College of Medicine, Mayo Clinic Hospital, Scottsdale, Arizona.
Accepted December 20, 2011.



S,(+)-Ketamine hydrochloride R,(−)-Ketamine hydrochloride

FIG. 1. S (+) and R (−) ketamine.

bind to the NMDA receptor and trigger the opening of calcium channels,[14] leading to other intracellular phenomena such as guanosine triphosphate mediated hydrolysis of phospholipids, and the generation of diacylglycerol and inositol 1,4,5-triphosphate (IP3), both of which foster the further accumulation of calcium in the cell. Diacylglycerol (DAG) also mediates the production of protein kinase C[15] which in turn generates nitrous oxide production, which acts at the synapse to cause the release of more excitatory amino acids.[16] A positive feedback loop is created as more activation of the NMDA receptor occurs because of the influx of excitatory amino acids. Activated protein kinase C diffuses to neuronal membranes and this binding correlates with both hyperalgesia and opioid tolerance.[17] Agents that block the translocation of protein kinase C from cytosol to the neuronal membrane reduce morphine tolerance.[18]

Ketamine Receptor Interactions

Ketamine interacts with several receptors that are important for pain management. The most important is the NMDA receptor. Ketamine also interacts with opioid receptors, norepinephrine and serotonin transporters, and ion channels.

NMDA receptor

Ketamine is described as a noncompetitive NMDA receptor antagonist, which means the drug requires an open channel so ketamine can access its binding site in the channel.[19] Ketamine has a high affinity for the NMDA receptor with a Ki of 0.9 uM for the S isomer and 2.5 uM for the R isomer.[20]

Opioid receptors

Ketamine interacts with opioid receptors. S-ketamine has affinity nearly equivalent to that of morphine for the μ and δ opioid receptors, with Ki's of 28 uM and 24 uM, but weaker affinity for the χ opioid receptor.[20] The R isomer has a weaker interaction with opioid receptors, with Ki for the μ, δ, and κ opioid receptors of 83, 60, and 286 uM, respectively.[20] The analgesic effect of ketamine is *not reversed* by naloxone, and the contribution of ketamine's interaction with the opioid receptors in the production of analgesia is not known.[21]

Other receptors

Ketamine has a weak action with muscarinic receptors with Ki of 125 uM and 91 uM with the S and R isomers, respectively.[20] Ketamine has weak interactions with dopamine, norepinephrine, and serotonin receptors. The affinity of ketamine for ion channels is weak.[20]

Formulations

Ketamine is available as an intravenous solution, which can also be administered orally, rectally, or intranasally.[22] When given orally, the intravenous formulation is used with a flavor additive. Ketamine can be stored at room temperature and can maintain its potency for more than 30 days. S-ketamine is also available in Europe as the commercially available pharmaceutical preparation and is also prepared in an aqueous solution.[23] Racemic ketamine is available in concentrations of 10 mg/mL, 50 mg/mL, and 100 mg/mL.

Compatibility

Ketamine is compatible with midazolam when mixed in normal saline. Ketamine is also stable when mixed with dexamethasone (low doses), haloperidol, opioids, ketorolac, and metoclopramide.[24]

Methods of Delivery and Modes of Administration

Ketamine has been administered for cancer pain by the oral, intravenous, and subcutaneous routes. The topical route has been evaluated for neuropathic pain. Ketamine is FDA approved for intramuscular and intravenous administration for induction of anesthesia prior to administration of other anesthetic agents.[25]

Pharmacology and routes of administration

The bioavailability of ketamine varies according to the route of administration. Intranasally, it is 25% to 50%, and the intramuscular bioavailablility is 93%.

Orally administered ketamine

The oral bioavailability is 17%, and the onset of action of ketamine is 15 to 20 minutes. The half-life of ketamine is 2.5 to 3.0 hours. Ketamine has protein binding of 20% to 30%.[26]

Pharmacologically, there are no major differences in the characteristics between the isomers.[27]

Intravenous route/subcutaneous route

Intravenous onset of action is within seconds and subcutaneously the onset of action is 15 to 20 minutes.[3] The half-life is two to three hours for both routes.[3]

Intranasally administered ketamine

When given by the intranasal route, ketamine has a bioavailability of 25% to 50%. Intranasal administration of

TABLE 1. CONTROLLED TRIALS OF KETAMINE FOR PAIN

Trial	*Pain type*	*N*	*Route/method*	*Endpoints*	*Outcomes*
Mercadante[53]	Cancer pain	10	intravenous, randomized, double-blind, crossover, double-dose study; two doses of ketamine	NRS 0 to 10; adverse effects categorical scale 0-3; MMSE 0–30; blood pressure at endpoints	ketamine but not placebo significantly reduced the pain intensity in almost all the patients at both doses; analgesia dose dependent; adverse effects dose dependent
Lauretti[54]	Cancer pain; run-in phase with opioid doses adjustment and adjuvants to keep pain <4 on NRS	60	pts with pain scores >4 randomized to groups (additional opioids), dipyrone, ketamine (0.5 mg/kg) as add-on to existing therapy	VAS scores, daily morphine consumption on days 1, 5, 10, 15, 20, and 30 were compared among groups	statistically less opioid consumption in the ketamine and nitroglycerin groups
Mitchell[56]	Vascular pain	35 18 ketamine (0.6 mg/kg over 4 hours); 17 placebo	intravenous; 48 h run-in with opioid titration, adjuvants allowed before randomization	BPI at entry, end of the run-in, 24 h after the infusion, and 5 days post infusion	statistically improved pain control ketamine group at 24 hours and 5 days
Sigtermans [57]	CRPS	60	placebo or ketamine by continuous infusion; inpatients; drug infusion rate started at 1.2 μg/ kg min^{-1} with titration; previous medications for pain allowed	NRS 0-10 during the 12-week study period; secondary outcomes of functionality and signs of neuropathic pain	pain scores were statistically lower in ketamine group at 11 weeks; statistical significance lost at 12 weeks; functional improvement did not follow the improvement in pain scores
Backonja[59]	peripheral neuropathy (N=3); central pain syndromes (N=3)	6	0.25 mg/kg ketamine IV or placebo IV on two separate occasions the same day; dose escalation allowed	VAS pain ratings; neurologic exam	dose dependent improvement in neuropathic pain
Lynch[61]	diabetic neuropathy, postherpetic neuralgia, or postsurgical/ posttraumatic neuropathic pain	92	topical placebo (vehicle only), 2%, amitriptyline, 1%, ketamine 1%, combination of 2% amitriptyline and 1% ketamine. 22-	pain intensity NRS, McGill Pain Questionnaire, exam for sensory abnormalities	no difference between groups; main adverse effect: skin irritation
Finch[63]	sensory disturbances due to CRPS	20	double-blind placebo-controlled crossover trial; topical creams, placebo, or 10% ketamine separated by at least 1 week.	detailed sensory examination before and after application	ketamine inhibited allodynia and hyperalgesia that was present at baseline; no systemic absorption

BPI, brief pain inventory; CRPS, complex regional pain syndrome; MMSE, Mini-Mental State Examination; NRS, numerical rating scale; Pts, patients; VAS, visual analog scale.

ketamine is associated with a rapid onset of action, with plasma peaks in 15 minutes, and rapid decline after 1 hour. Bioavailability after intranasal administration is 25% to50%.[28] The intranasal route has been studied for breakthrough pain.[29]

Intrathecally or epidurally administered ketamine

Ketamine has been administered both intrathecally and epidurally. When given intrathecally, ketamine can reduce intrathecal opioid requirements.[30] There are no pharmacokinetic studies for the administration of ketamine, either intrathecally or epidurally. One would presume given the lipophilic nature of ketamine that the epidural routes would be pharmacokinetically similar to parenteral routes. One report suggests that the duration of analgesia via the epidural route is anywhere from 30 minutes to 6 hours.[31] A double-blind comparison of epidural ketamine versus epidural morphine showed that morphine was more potent, with longer periods of analgesia.[32]

Rectally administered ketamine

Rectal ketamine has been administered in the pediatric population as a premedication. Pharmacokinetic studies suggest that the drug has a longer half-life than when given parenterally.[33]

Other routes of administration

Ketamine has been administered transdermally (post-op setting),[34] iontopheretically,[35] however there have been no formal phamacologic studies for these routes. Ketamine has been given topically and has not been shown to be absorbed systemically.[36]

Metabolism

Eighty percent of ketamine undergoes hepatic metabolism via cytochrome 3A4 (N-methylation) to its principle metabolite norketamine.[3] Norketamine is produced in greater quantities after oral administration, suggesting a substantial first-pass effect. Norketamine is an active agent, and contributes to the analgesic effect of ketamine. Urinary excretion of unmetabolized drug is 4%.[37]

Dosing in Special Populations

Renal failure

There is no information regarding the safety and dosing recommendation in using ketamine in renal insufficiency. Norketamine can accumulate in renal insufficiency.[38] Ketamine is minimally removed during dialysis, which is consistent with it being a lipophilic agent.[38]

Hepatic insufficiency

There is no information regarding the safety and dosing recommendation in using ketamine in hepatic insufficiency. Ketamine has little impact on hepatic blood flow, even in large doses.[39]

Adverse Effects of Ketamine

Adverse effects associated with ketamine are dose related, with the most frequent occurrences at anesthetic doses (> 1 mg/kg). At anesthetic doses, the principal adverse effects are psychotomimetic, with frequencies ranging from 5% to30%,[40] and become less frequent with lower doses.[26] Psychotomimetic effects are characterized as emergence phenomena, effects on cognition, and psychiatric effects.[41] Emergence phenomena are described as vivid dreams, hallucinations or floating sensations, and visual spatial disorders. The psychiatric manifestations of ketamine use have included blunted affect, emotional withdrawal, thought disorders, and delirium. The incidence of psychiatric manifestations is increased in patients with a psychiatric history. The next most common group of adverse effects is cardiovascular in nature and include increases in heart rate, blood pressure, systemic vascular resistance, and pulmonary vascular resistance.[42] Ketamine does have a negative inotropic effect on the heart, but this is overshadowed by catecholamine release.[43] Gastrointestinal adverse effects include nausea, vomiting, anorexia, and hypersalivation.[41] Low-dose ketamine is associated with less-frequent adverse effects. When examining the largest studies using low-dose ketamine in the palliative medicine population, most common adverse effects involve the central nervous system. In a study using burst ketamine, the incidence of psychotomimetic adverse effects predominated in the 300 to 500 mg/dosing range.[44] Cardiovascular adverse effects occurred sparingly with 1 in 31 patients. In the same study there were minimal gastrointestinal adverse effects. In the study using bolus ketamine (0.5 mg/kg), of nine patients, two had anorexia, four had nausea, one had vomiting, and the others had no adverse effects.[45] Respiratory depression is rare with ketamine at anesthetic doses and is unlikely to occur at subanesthetic doses.[46] There is little evidence that ketamine impairs gastrointestinal transit.[26] Urinary symptoms in the form of ulcerative cystitis are increasingly recognized with ketamine abuse.[47] Its incidence in palliative care patients is yet to be determined.

Drug Interactions

There have been no reports of clinically significant drug interactions with ketamine. Ketamine may be given simultaneously with opioids, neuroleptics, sedative hypnotics, or antidepressants.

Contraindications to Ketamine Use

Recommendations in the literature have suggested that ketamine is contraindicated in the presence of increased intracranial pressure (ICP), seizures, and "neurologic impairment."[48] Relative contraindications include hypertension, cardiac failure, and previous cerebrovascular accidents. Evidence suggests that ketamine is indeed safe to use in the presence of ICP. One study of 20 patients requiring craniotomy for brain tumor or cerebral aneurysm involved measurement of cerebral blood flow and ICP parameters, while patients received ketamine as part of their anesthesia regimen at *anesthetic* doses (1 mg/kg). The ICP actually decreased after the initiation of ketamine in this study.[49] Another study found that children with sustained, elevated ICP (> 18 mm Hg) who received ketamine for invasive procedures showed no worsening of ICP with the use of ketamine. Ketamine is contraindicated in patients where blood pressure elevations might pose a threat, such as in patients with severe cardiovascular disease, recent myocardial infarction, or cerebrovascular

accident,[46] although it should be noted that the *low-dose ketamine* trials did not show any substantial issues with increased blood pressure when given at subanesthetic doses. Blood pressure issues may become an issue when dose is increased. Ketamine should be avoided in patients with severe psychiatric disorders.[48] There is preliminary evidence, however, for its benefit in the treatment of depression.[50] Reports have linked ketamine as being a cause of seizures,[51] and as an agent with potential use for the treatment of seizures.[52]

Ketamine for Pain Control

Randomized controlled trials for ketamine have been conducted in cancer-related neuropathic pain, regional pain syndromes (such as the complex regional pain syndrome), chronic neuropathic pain syndromes (including postherpetic neuralgia), and ischemic pain. Topical ketamine has been evaluated for neuropathic pain. Ketamine has been evaluated for incident pain.[55]

Randomized Controlled Trials

Cancer-related neuropathic pain

Mercadante and coworkers[53] evaluated the analgesic effect of parenteral ketamine in cancer-related neuropathic pain. The patients had been on morphine only for pain control, with an average dose of 169 mg/d. Ten cancer patients were randomized to boluses of subanesthetic doses of ketamine (0.25 mg/kg or 0.50 mg/kg) or placebo, when pain was unrelieved by morphine. Pain was assessed with a patient-reported numeric rating scale; other symptoms such as nausea, vomiting, sedation, confusion, and dry mouth were assessed with categorical scales. Before entry into the trial, a baseline Mini-Mental State Examination (MMSE) was done, and vitals were taken at 30, 60,120, and 180 minutes after ketamine administration. Ketamine at both study doses was able to reduce pain intensity, while placebo was not. There was a dose-response relationship with respect to analgesic effect. Psychotomimetic effects consisted of hallucinations in four patients. These hallucinations were successfully treated by diazepam 1 mg intravenously. Two patients experienced an "empty head" feeling. Patients receiving the higher dose of ketamine experienced more drowsiness and at 30 minutes had lower MMSE scores.

Cancer pain

Lauretti and coworkers[54] evaluated ketamine as an adjuvant analgesic in a trial of 60 patients who had cancer pain. All patients were receiving oral amitriptyline (50 mg) at bedtime and had pain that did not respond to step 1 (nonsteroidal drugs) or step 2(tramadol) analgesics, and had been receiving dose-adjusted morphine to keep the pain (rated on a numeric scale) at less than 4. The maximum dose of morphine given was 80 to 90 mg per day. Randomization occurred when pain scores were greater than 4. The study did not do subset analysis on type of pain, but one-third of patients had head and neck cancer. Patients were randomized to receive 20 mg of additional oral morphine (12 h intervals), 500 mg oral dipyrone (6 h intervals), 0.5 mg/kg oral ketamine (12 h intervals), or a patch of 5 mg nitroglycerin daily (5 mg transdermal patch). After the test drug was introduced, patients used breakthrough morphine in addition to the 80 to 90 mg daily dose, to keep pain measured on the numeric rating scale less than 4. In this pilot study, ketamine was associated with decreased opioid consumption on day 10, 15, 20, and 30, compared to placebo.

Ischemic pain: Single infusion of ketamine

Mitchell and Fallon[56] conducted a randomized, double-blind trial of opioid therapy, along with either low-dose ketamine or placebo, to control pain from vascular insufficiency. Eighteen patients received the opioid-ketamine combination and 17 received the opioid-placebo combination. Analgesia was measured by the Brief Pain Inventory. Improvements in pain in those receiving ketamine were 15% at 24 hours and nearly 20% by day five. Pain relief decreased *in the placebo group* by 2% and 8% at 24 hours and five days, respectively ($P < 0.05$). significant improvements were seen in activity ($P < 0.03$) and quality of life ($P < 0.04$). The study showed that ketamine –opioid combinations are useful in vascular ischemia.

Other pain syndromes: Randomized controlled trials

Complex regional pain syndrome. A randomized double-blind placebo controlled trial evaluated ketamine for chronic pain in 48 patients with complex regional pain syndrome type 1 (CRPS-1). Patients were randomized to receive either ketamine (S (+)-ketamine) starting on day one at 5 mg/h with adjustments up to three times daily (max. thrice daily) to maximum doses of 30 mg/h for a 70 kg patient or identical placebo with the same doing regimen. Dose escalations were adjusted for analgesic response or adverse effects.[57] The primary outcome of the study was the pain score on a numeric rating scale (NRS) 0-10 during the 12-week study period. The mean amount of ketamine required was 22 mg/hr. Pain scores were lower in the patients who received ketamine ($P < 0.001$) for 11 weeks, but at week 12, significant pain differences between the groups had diminished ($P = 0.07$). Functional improvement did not follow the improvement in pain scores, and patients receiving ketamine more often experienced psychotomimetic effects (76% versus 18%, $P < 0.001$).

Post-herpetic neuralgia. Eide and coworkers evaluated analgesic thresholds and evidence of neuropathic changes before and after the administration of ketamine (0.15 mg/kg), morphine (0.075 mg/kg) or saline in eight patients experiencing postherpetic neuralgia.[58] Patients manifested abnormal thresholds for warm, cold, heat pain, or tactile sensation in the affected area. Neither drug had an effect on thresholds for warm, cold, heat pain, or tactile sensation. Ketamine was able to normalize burning dysesthesias in four patients. Ketamine had a greater impact on pain than morphine, and both drugs were able to lessen allodynia. Windup-like pain was inhibited by ketamine, but not morphine. Adverse effects such as fatigue, feelings of unreality, and dizziness were the most bothersome symptoms experienced by patients receiving ketamine.

Chronic neuropathic pain syndromes. Backonja and coworkers[59] evaluated the use of ketamine (0.25 mg /kg intravenously) in six patients with chronic neuropathic pain. Pain syndromes consisted of peripheral neuropathy ($N = 3$) and central pain syndromes ($N = 3$). After dosing, all three

patients with neuropathic pain and two of three with central pain had decreases in pain scores. Other features of neuropathic pain, such as allodynia and hyperalgesia, improved in five patients. One of the patients with peripheral neuropathy did not respond to ketamine. In responders there appeared to be a dose-response relationship, as two of the patients were given subsequent dosing and had lower pain scores with the increased dosing. Adverse effects in the five patients who received ketamine bolus were mild and did not lead to discontinuation of therapy.

Topical Ketamine: Neuropathic Pain

While initial pilot studies did not show efficacy for topical ketamine for neuropathic pain,[60] a subsequent randomized placebo-controlled trial evaluating the efficacy of topical ketamine for neuropathic pain by the same authors showed different results. Lynch and coworkers[61] compared one of four creams (placebo, 2% amitriptyline, 1% ketamine, or 2% amitriptyline–1% ketamine combined) in 92 patients with diabetic neuropathy, postherpetic neuralgia, or postsurgical/posttraumatic neuropathic pain with symptoms of allodynia, hyperalgesia, or pinprick hypesthesia. The primary outcome measure was change in average daily pain intensity (baseline week versus final week) using an 11-point numerical pain rating scale. Secondary outcomes included the McGill Pain Questionnaire, measures of allodynia and hyperalgesia, and patient satisfaction. In all groups there was a reduction in pain score by 1.1 to 1.5 units without differences between the groups. Those electing to enter an open-label portion of the study were found to have an average reduction in pain scores by one-third, with five patients experiencing a 50% or greater reduction in score and one patient reporting complete elimination of pain. At one year the average pain reduction was 37%, with 40% achieving a greater than 50% reduction and two achieving complete elimination of pain. Nearly 90% of the patients reported satisfaction with the treatment. Surprisingly, five patients were able to discontinue oral analgesics. No systemic absorption was detected. A follow-up study evaluated topical amitriptyline and ketamine (4% and 2%) in 118 patients with postherpetic neuralgia with study arms consisting of 4% amitriptyline/2% ketamine, 2% amitriptyline/1% ketamine, or placebo.[62] More patients (46%) experienced a greater than 30% reduction in their pain scores than the low-dose arm (26%) and placebo (19%). The duration of this effect was for three weeks. Only 10% of the patients had detectable drug levels from the topical medication and these levels were considered minimal and noncontributory to the clinical effect observed.

Topical Ketamine and CRPS

Finch and coworkers[63] evaluated topical ketamine for the management of sensory disturbances due to CRPS. The study was a double-blind, placebo-controlled crossover trial, in which 20 patients took a detailed sensory examination consisting of testing with touch, pressure, and temperature stimuli, in the distribution of the CRPS. The percentage of topical ketamine compared to placebo was 10%. Peripheral blood was drawn to assess for the absorption of ketamine into the bloodstream (one hour after application). Ketamine inhibited allodynia and hyperalgesia that was present at baseline. There was no systemic absorption with the 10% topical formulation.

Uncontrolled Trials: Burst Ketamine

Two studies have evaluated the technique of "burst ketamine" for refractory pain, which uses escalating doses of ketamine based on clinical response. In this technique patients are started with a ketamine dose of 100 mg/24 h intravenously or subcutaneously, and continue with this dose if they achieve satisfactory analgesia, for three days, when ketamine is then stopped. If there is not a satisfactory analgesic response after 24 hours, the dose is increased to 300 mg, and depending on analgesic response, the dose is either maintained at that dose or further increased to 500 mg per day. Eligible patients in both studies had pain that they rated at least 4 out of 10 on an NRS, and were not responsive to nonsteroidal antiinflammatory drugs (NSAIDs), opioids, or neuropathic agents. Endpoints in the studies were: achievement of complete pain relief, 50% or greater reduction in the pain score associated with a 50% or greater reduction in opioid dose, 50% or greater reduction in the number of breakthrough analgesics required, and improvement in Eastern Cooperative Oncology Group (ECOG) performance status by at least one point. The first study, an open-label audit, by Jackson and coworkers,[44] evaluated 17 patients with somatic pain and 23 patients with neuropathic pain. Fifteen of 17 patients with somatic pain responded and 14 of 23 patients with neuropathic pain responded. In five patients it was unclear if ketamine contributed to the analgesic effect. When ketamine was stopped, the analgesic effect was maintained in 24 of 29 patients for up to eight weeks. Of the initial responders, five required the restarting of ketamine for pain control and three required ketamine until death two to four weeks later. The main adverse effects were psychotomimetic, especially in patients with an increase of 300 to 500 mg per day. Of those experiencing adverse effects, eight were responders and four were not. In those four, ketamine was stopped. In the responders, dose reduction lead to improvement in adverse effects in three; whereas five preferred the adverse effects to the reduced dose.

Recently a multicenter prospective single-arm open-label study[69] reevaluated the effectiveness of the burst technique. This study consisted of 44 patients with cancer and the same eligibility criteria as in the first study. Patients all had cancer pain with breast and lung cancer comprising the majority; there were three patients with multiple myeloma. Sixty-four per cent had neuropathic pain with 32% having somatic pain (bone pain). Forty-four patients were evaluable, and preketamine opioids consisted of step 3 opioid such as morphine, fentanyl, oxycodone, and hydromorphone. Twenty-two of 44 patients were classified as responders with four getting an NRS pain score of 0. Seventeen of 22 responders needed a ketamine dose of more than 300 mg/day. Sixty-one percent of all patients experienced an adverse effect with no difference between responders and nonresponders. The grade 3 and 4 toxicities occurred in those requiring 300 mg or more per day of ketamine. The most common grade 3 toxicity was injection site toxicity and the most common grade 4 toxicity was hallucination. Cardiovascular adverse effects were minimal. Follow-up with 13 patients for one month showed that 11 of these had continued reductions of their pain scores by 50% for at least two weeks with one patient responding for three months. Three responders were successfully retreated.

Methods of Administration

Ketamine dosing may be preceded by a test dose, which is used to predict for analgesic response and identification of adverse effects. Test doses are not required to initiate ketamine therapy.

Test dose

Test doses have been given by multiple routes. The amount of ketamine recommended for the test dose has ranged from 5 mg intravenously or subcutaneously to 20 mg orally. When the test dose is given, there is assessment of adverse effects and analgesic response. Recently Mao and coworkers[64] evaluated the test dose as a prognosticator for response to other NMDA antagonists. They used a dose of 0.6 mg/kg intravenously. Patients were monitored closely and observed for psychotomimetic adverse effects. Prophylactic haloperidol or a benzodiazepine can be given for the test dose and subsequent doses to manage untoward psychotomimetic adverse effects.

Schedule of administration

When given as a bolus by either the oral subcutaneous or intravenous route, ketamine can be dosed from six to eight hour intervals.

Ketamine dosing

Both nonweight-based and weight-based dosing have been used to start regular dosing of ketamine.[27] Ketamine has been administered also as a bolus and as a continuous infusion.

Weight-based dosing bolus

Weight-based dosing has ranged from 0.1 mg/kg to 0.8 mg/kg which is *below* the anesthetic dose of ketamine (1 mg/kg). An effective starting dose for ketamine appears to be 0.5 mg/kg.[53] This dose can be used for intravenous bolus, oral, or subcutaneous boluses.

Nonweight-based dosing

Nonweight-based dosing usually begins with dosing in the range of 100 mg of ketamine given over 24 hours by continuous infusion or bolus in divided doses.[65] Techniques such as burst ketamine have incorporated a daily escalation of 100 mg if this starting dose is not effective.

Breakthrough ketamine doses

Ketamine is not well studied as a breakthrough analgesic, but there have been recommendations for it to be used at doses similar to opioid breakthrough dosing.

Some authors[66] recommend giving extra doses for breakthrough pain (1/10 to 1/6 of the oral or subcutaneous daily dose or 5 to 10 mg IV) to cover wound dressing changes.

Methods of dose adjustments

Dose adjustments can be made quickly and according to pain intensity, as with opioids.[66] Downward adjustment of the opioid should be considered if sedation occurs with escalation of the ketamine dose, as this may suggest reversal of opioid tolerance.[66] There are no guidelines to establish how much of a dose reduction of opioid is required when sedation occurs.

Dose conversions

A recent prospective study found that that when switching from oral to parenteral ketamine and vice versa, a ratio of 1:1 is acceptable,[67] which contradicts previous recommendations suggesting a 50% reduction in the intravavenous dose when switching from the oral route.[37,68]

Discontinuation of Ketamine

Ketamine can be safely discontinued without withdrawal. Analgesic effect can persist when the drug is stopped.[44] Opioid requirements after cessation of ketamine have not been studied.

Prophylactic Management of Adverse Effects

The most common adverse effects associated with the initial use of ketamine are psychotomimetic effects. Recommendations for the management of these effects include the use of a benzodiazepine such as lorazepam or midazolam, or a butyrophenone such as haloperidol.[27] These agents can be discontinued if there are no adverse effects with ketamine use, or can be instituted with dose escalation and the need for higher doses of ketamine. Some authors advocate the use of these agents, to be given simultaneously for the initial doses of ketamine, and can be stopped if the patient experiences no psychotomimetic effects.[48] Glycopyrrolate has been advocated for other adverse effects such as increased secretions.[27]

Monitoring of Patients

Recommendations for monitoring patients receiving ketamine include vital signs, sedation, and pain score one hour after initial administration, every four hours for the first day, and every eight hours thereafter. This should be repeated after dose escalations.[70] Cardiovascular adverse effects occur infrequently when ketamine is given at subanesthetic doses.[44]

Pharmacoeconomics

Pricing[71] for a 10 mL vial of 50 mg/ml concentration is as follows:

1 vial, $16.99;
2 vials, $24.98;
3 vials, $29.97;
4 vials, $39.96;
5 vials, $49.95;
6 vials, $59.94

Conclusion

Ketamine is a lipophilic general anesthetic that has been found to be a useful analgesic when given at subanesthetic doses for patients with cancer-related neuropathic pain, neuropathic pain, and ischemic pain. The analgesia achieved by ketamine is not mediated by opioid receptors. The drug is lipophilic and easily absorbed, and has the advantage of topical administration. There is little risk for drug interactions. Ketamine has opioid-sparing properties through its ability to block the NMDA receptor with high affinity. This makes

ketamine a useful agent when there are difficulties with opioid responsiveness. Subanesthetic doses (< 1 mg/kg) seem to produce fewer adverse effects than anesthetic doses. However, with dose escalation, even when starting at subanesthetic doses, psychotomimetic adverse effects can occur at the daily dose of 400 to 500 mg. These psychotomimetic effects can be easily treated with haloperidol or short-acting benzodiazepines such as lorazepam. The preferred agent for management of psychotomimetic effects is unknown at this time, but most experience has been with either haloperidol or lorazepam. Randomized control studies have been done in patients with cancer pain and fairly low morphine equivalent doses. Patterns that have emerged are that ketamine is indeed capable of opioid sparing. Another intriguing feature of ketamine is that analgesia can persist when the drug is discontinued. Unfortunately, the available trials have small numbers.

Author Disclosure Statement

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