Low dose ketamine in the age of opioids

The opioid epidemic has been a conundrum of historic proportions for the house of medicine imposing significant disruptions on emergency medicine practice. Emergency physician influence on the opioid epidemic may be quite limited [1,2]. Notwithstanding, our specialty is significantly affected and solutions must be sought. Indeed, emergency physicians find themselves caught between customer satisfaction surveys, hospital administration expectations, Joint Commission trends and other external forces with respect to chronic pain management. Numerous alternative approaches to pain management for the opiate tolerant patient presenting with pain to the emergency department have emerged over recent years but there is no consensus on a most effective strategy. In fact, there is nothing but diversity with approaches ranging from “Dilaudid-Free” emergency departments to nurse-driven protocols utilizing high dose hydromorphone for pain control for the same or similar patients.

Sundry variables complicate the dilemma. The emergency department patient population is one of the most diverse in medicine. Emergency physicians must address acute pain conditions and chronic nonmalignant pain syndromes typically within a single shift with discrimination variables often necessarily subjective. Further, there is little consensus even within individual groups; emergency physician opioid prescribing habits vary significantly even within in a single practice [3]. Emergency physicians reside in a “goldfish bowl” where physician medical decisions are subject to external forces which may not coincide with best practice. Any monolithic approach or protocol driven application to our diverse patient population presenting with acute or chronic versus chronic pain is likely to be insufficient.

The authors of the article in this issue of AJEM, “Low Dose Ketamine Use in the ED: A New Direction in Pain Management,” provide a timely review of an adjunctive approach to acute exacerbation of chronic pain and acute pain management. Low-dose ketamine (LDK) has not yet reached the stage of widespread acceptance or utilization but it is “ready for prime time” consideration. LDK is another “arrow in the quiver” for pain management for selected ED patients, particularly for patients opioid tolerant or dependent.

Pourmand et al. do raise several important issues to be considered for integration of LDK into our everyday practice. First, patient safety is paramount. The relevant literature supports the safety of ketamine at sub-dissociative doses, as detailed in the review. Nursing protocols for managing and monitoring patients receiving LDK have been successfully and safely implemented in some institutions [4]. As emergency nursing practice varies by department, hospital-specific protocols are desirable. Adequate monitoring of patients receiving LDK with or without opioids is essential. Historically, controversy regarding ketamine’s use in the emergency department has occurred but political issues have largely been surmounted [5,6].

Of course, emergency physicians are loath to advocate another drug to mediate opioid over-use in the emergency department that has similar abuse potential. Ketamine is not a common drug of abuse in the United States compared with opioids [7]. However, ketamine abuse is a significant problem internationally, particularly in China and Southeast Asia, where it is frequently cited within the top three most commonly used illicit drugs [8,9]. When used recreationally, ketamine is most often procured as a powder obtained from pharmaceutical sources (i.e., veterinary or medical stock), large-scale international drug trafficking, and various internet suppliers [10]. Though the exact mechanisms of addiction are poorly-defined for ketamine, the drug clearly demonstrates reinforcing properties and the risks for misuse, addiction, and diversion which must be considered. However, there is nothing to suggest that the emergency department prescription of ketamine is associated with an increased incidence of subsequent abuse.

Cost savings and the HEART pathway: The author responds

We very much appreciate the correspondence regarding our recent article describing a retrospective cost-analysis of the HEART Pathway in the context of the larger randomized trial describing its use in a US cohort. While we should always aspire to examining its use in a US cohort. While we should always aspire to examining the generalized applicability of our study.

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References


Cost savings and the HEART pathway: The author responds

Robert F. Riley
Division of Cardiology, University of Washington Medical Center, 1959 NE Pacific Street, Seattle, WA 98157, United States
E-mail address: rfriley@uw.edu.

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Ketamine’s general safety and appropriate prescription by emergency physicians, as well as, its acute therapeutic use in the emergency department administration are no longer issues of debate and medical politics. On a scientific basic, LDK should face less controversial integration as an adjunctive therapy integrated into the management of acute and chronic pain in the emergency department.

Richard M. Sobel, MD, MPH
Southern Regional Medical Center, Riverdale, GA, United States
Corresponding author:
E-mail address: rsobel@aol.com
Alaina R. Steck, MD
Department of Emergency Medicine, Emory University, Atlanta, GA, United States

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Low dose ketamine use in the emergency department, a new direction in pain management

1. Introduction

The US is amidst of an epidemic of opioid misuse, abuse, and diversion [1–3]. In the past decade, a 300% increase in opioid analgesic prescribing has been accompanied by a three-fold increase in drug overdose deaths and a two-fold increase in emergency departments (ED) visits for opioid misuse and abuse [4,5]. Opioid analgesics are commonly administered and prescribed from the ED; however, the ED’s contribution to the current epidemic remains unclear [6]. In addition, patients are commonly treated with opioid analgesics for a variety of conditions in the outpatient setting and may be tolerating, making pain management in the ED more challenging. The use of high doses of opioid analgesics has been associated with life-threatening adverse effects, secondary to respiratory depression [7,8]. In an effort to curb opioid misuse and abuse, as well as to promote safe and rational opioid prescribing, there has been a renewed interest in alternative non-opioid analgesics.

Low dose ketamine (LDK) has emerged as a safe and effective non-opioid alternative for patients with chronic or refractory as well as acute pain. Ketamine is a distinct pharmacologic agent with a unique mechanism of action and adverse effect profile. It is not simply an “opioid substitute”. LDK can be used in the ED in a variety of clinical situations. It can be used for patients who need analgesia prior to an awake procedure. LDK can also be used in the setting of an acute exacerbation of pain in patients that are at high-risk of adverse effects from opioids and when other non-opioid therapies (such as non-steroidal anti-inflammatory drugs) have failed. Ketamine may also be useful to treat acute pain in the setting of hemodynamic instability [9]. Some particularly challenging groups are patients presenting with acute exacerbations of nonmalignant chronic painful conditions such as sickle cell anemia [10], dento-facial pain syndromes [11], headaches [12], axial skeletal pain [13, 14], and gastroparesis. Patients with malignant and non-malignant chronic pain are often on high-dose opioid analgesics at baseline, making their pain difficult to manage in the ED. Ketamine infusion may be of utility in opioid-tolerant patients with acute intractable exacerbations of chronic pain by a proposed mechanism of re-sensitizing to their opioid regimen [15]. In recent years, there has been a renewed interest in and study of ketamine in the ED. This review will focus on the use of LDK for the acute treatment of pain, with a focus on its utilization in the ED setting.

2. Ketamine mechanism of action and pharmacokinetics

Ketamine is a well-known N-methyl-D-aspartate (NMDA) receptor antagonist. One of the normal functions of the NMDA receptor is to potentiate painful stimuli, which may lead to a “hyperalgesia” or “central sensitization”. Ketamine’s analgesic effect has been attributed, in part, to its ability to block this sensitization [16]. Ketamine is a non-competitive NMDA receptor antagonist with a, “slow off rate” causing a prolonged tonic blockade of the receptor contributing to long lasting analgesic effects [17]. Ketamine also has direct effects on the delta opioid receptor and acts to augment opioid mu-receptor function [18]. The way by which ketamine augments opioid receptor function has been attributed to downstream effects involving the extracellular signal-regulated kinase 1/2 (ERK1/2). Ketamine potentiates opioid induced ERK1/2 phosphorylation, requiring lower opioid doses for equal phosphorylation [18]. Ketamine has also been shown to delay desensitization and improve re-sensitization of opioid receptors resulting in prolonged overall effect of opioid stimulation, which may be useful in patients with opioid-related hyperalgesia [18]. Ketamine has a high first pass metabolism. The oral availability is between 17 and 24% for racemic ketamine and 8–11% for S-ketamine [19]. Intramuscular bioavailability is 90%–93%. Ketamine is initially distributed to highly perfused tissues such as the brain, lungs, and heart where it can reach up to 5 times plasma concentrations [20]. Ketamine is metabolized by CYP3A and CYP2B6 through N-demethylation to norketamine, which has about one-third of the activity of ketamine [19,20]. The only absolute contraindication to ketamine is for patients who have an allergy to ketamine. Relative contraindications include: moderate to severe hypertension, congestive heart failure, pregnancy, or acute alcohol intoxication [20]. Traditionally, there has been a theoretical concern that ketamine can cause increased intracranial pressure, but recent studies have demonstrated ketamine does not significantly increase intracranial pressure [21,22,23]. Ketamine use has been reported to result in an emergence delirium or emergence reaction. This phenomenon includes alterations in mood and body image, dissociative experiences, vivid dreams and illusions, and delirium. This reaction may be more frequent with larger doses of ketamine, in patients older than 16 years of age, and in female patients [24].