Ketamine—What Is Old Is New Again

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KETAMINE, A CHEMICAL derivative of phencyclidine, was first administered to human volunteers in 1964. As the dose was increased, ketamine's effects ranged from "conscious but 'spaced out'" to general anesthesia. Most subjects described "strange experiences like a feeling of floating in outer space and having no feeling in their arms or legs."[1] In 1970, ketamine was approved by the US Food and Drug Administration as an anesthetic. With the availability of newer agents such as propofol, ketamine is rarely indicated as an anesthetic. Today, the primary role of ketamine is (1) to provide analgesia and sedation, (2) as an adjunct of multimodal analgesia (acute pain, chronic pain), and most recently (3) as treatment for major depressive disorder.[2,3]

Physicochemical Characteristics and Pharmacodynamics

In the United States, ketamine is available as a racemic mixture of the (*S*)(+) and *R*(−) isomers, with the (*S*)(+) isomer having fourfold the activity at the *N*-methyl-D-aspartate (NMDA) receptor as the (*R*)(−) isomer. Ketamine has dose-dependent effects. In higher doses (1 to 2 mg/kg intravenous [IV]), ketamine produces a "dissociative anesthesia" or cataleptic state—the eyes stay open and patients generally maintain many of their corneal, cough, and swallow reflexes. Analgesia is present, as well as amnesia although the amnesia from ketamine is not as profound as that produced by a benzodiazepine. Nystagmus occurs, lacrimation and salivation are common, and skeletal muscle tone increases often with purposeless muscle movements. At lower doses (0.2 to 0.8 mg/kg IV), ketamine produces sedation and analgesia. At even lower doses (0.15 mg/kg IV bolus or as a low-dose infusion), ketamine provides analgesia and reduces or delays opioid-induced tolerance and hyperalgesia.[4-6]

Mechanism of Action

The primary mechanism of action of ketamine is as an NMDA receptor antagonist.[3-5] By blocking NMDA receptors in the brain and spinal cord, ketamine (1) modulates central sensitization and wind-up (mechanisms of chronic pain), (2) reduces or delays opioid-induced tolerance and/or hyperalgesia, (3) potentiates opioid analgesia (subanesthetic doses), and (4) reduces presynaptic release of substance P in the spinal cord (Substance P and glutamate propagate pain signals). Other effects of ketamine include (1) modulating muscarinic acetylcholine receptors, potentially reducing pain sensitivity thresholds; (2) upregulating α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) receptors, potentially resulting in improved mood and emotional response to pain; and (3) modulating glutamatergic pathways involved in depression. These other effects of ketamine (eg, upregulating AMPA receptors) may change gene expression and protein regulation, possibly explaining why ketamine may continue to have beneficial effects after discontinuation.[3,7-9]

Pharmacokinetics

Ketamine is highly lipid soluble and rapidly distributed to the brain and other well-perfused tissues (distribution half-life is 2 to 4 minutes). Ketamine is then redistributed to muscles and peripheral tissues, and ultimately to fat. Ketamine undergoes extensive hepatic metabolism by the cytochrome P450 enzyme system. The combination of redistribution and hepatic metabolism accounts for ketamine's short duration of action (elimination half-life is 2 to 4 hours). Ketamine is metabolized to hydroxyketamine, norketamine, and dehydronorketamine. Norketamine is active, has a long half-life (12 hours), and reported to have antinociceptive actions.[4,6,8] The presence of

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norketamine may continue (from parent ketamine) the potentiation of opioid analgesia and prevention of opioid-induced tolerance and hyperalgesia.[9]

Role in Postoperative Pain Management

A wide variety of IV ketamine dosing regimens for perioperative analgesia have been studied. Laskowski et al[10] conducted a systematic review of randomized controlled trials that reported the administration of IV perioperative ketamine and measured postoperative analgesic use or pain. In an effort to account for the heterogeneity of dosing regimens, the authors narrowed the inclusion criteria (no regional anesthesia), used a random-effects model, and performed subgroup analysis. Their primary outcome was total postoperative opioid use; secondary outcomes included time to first analgesia use, pain scores, and adverse effects. Seventy studies met inclusion criteria, with 64 included in the quantitative analysis and the remaining 6 included only in the qualitative analysis. Ketamine was administered (1) in doses ranging from ≤0.5 mg/kg to greater than 1 mg/kg; (2) as a bolus alone, patient-controlled analgesia (PCA) alone, bolus ± PCA, and infusion ± PCA; and (3) preincision or postincision. Overall, ketamine reduced total opioid requirements and delayed the time to the first analgesic dose. Ketamine was most effective for thoracic, upper abdominal, and major orthopaedic surgeries. Despite higher opioid consumption, most placebo treatment groups (25 of 32; 78%) experienced more pain compared with ketamine treatment groups when ketamine was efficacious. The analgesic effect of ketamine was independent of the timing of administration (preoperative, intraoperative, or postoperative) when the anticipated postoperative visual analog score was greater than 7/10. Although ketamine was beneficial in some patients, it is not without risk. There were more neuropsychiatric adverse effects (eg, hallucinations and nightmares) in the ketamine treatment groups. Of note, the authors acknowledge that the significant heterogeneity of the studies remained a limitation of their review.[10]

Avidan et al[11] conducted a multicenter, international, randomized controlled trial to determine whether an intraoperative bolus dose of ketamine decreased delirium (as demonstrated in a small, single center trial[12]), pain, or both without increasing adverse effects. Patients aged 60 years or older undergoing major surgery (N = 672) were randomized to receive a single bolus dose of 0.5 mg/kg ketamine IV (N = 237), 1 mg/kg ketamine IV (N = 223), or equal volume of normal saline (N = 232) after induction of anesthesia and before surgical incision. Anesthetic technique was at the discretion of the anesthesia care provider. Trained members of the research team (blinded to the treatment group) assessed patients for delirium (primary outcome) using the Confusion Assessment Method or Confusion Assessment Method for the intensive care unit before surgery and twice a day for the first three postoperative days. At the same time, the research team assessed patients for pain using predetermined, validated pain assessment tools. There were no differences in pain intensity or postoperative opioid consumption between the groups over the entire study period (first three postoperative days). More patients in the 1 mg/kg ketamine reported hallucinations and nightmares than patients in the 0.5 mg/kg ketamine or placebo groups (P = .03). The authors concluded that administration of a subanesthetic (0.5 or 1 mg/kg IV) dose of ketamine to patients aged 60 years or older undergoing major surgery does not reduce postoperative delirium, pain, or opioid consumption. As noted by the authors, it is not uncommon that a large effectiveness trial such as this does not replicate the results of small trials, systematic reviews, or meta-analyses comprising small, often heterogeneous, studies.

When one considers the pharmacokinetics (fast onset, short duration) and the antinociceptive effects of ketamine, a continuous infusion of ketamine throughout surgery and continued into the postoperative period has been recommended (1) to prevent chronic postoperative pain in patients undergoing more invasive painful procedures[13,14] and (2) in patients on chronic opioids undergoing major surgery.[15,16] Clinically relevant analgesia with minimal adverse effects can be achieved with a postoperative infusion of 2 mcg/kg/min.[16,17] For adults, this typically corresponds to 10 mg/h infusion (~2.5 mg/kg/min for a 70 kg patient).[18] If necessary, upward titration of the postoperative infusion to ≥20 mg/h (~5 mcg/kg/min for a 70 kg patient) does not appear to increase the chances