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Review Article

Utility of Ketamine

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Abstract

In recent years, Ketamine has been hailed as a "miracle" treatment for depression and related disorders. The United States Food and Drug Administration (FDA) approved the S-enantiomer of ketamine (esketamine), as the first antidepressant in a new class for treatment-resistant depression in 2019 (20). Emerging evidence has suggested that the use of ketamine as both a therapeutic and recreational substance is shifting. This article will highlight several key points regarding the usage of ketamine for physicians, policy makers, as well as patients and families.

Keywords: food and drug administration; physicians

Introduction

In recent years, Ketamine has been hailed as a "miracle" treatment for depression and related disorders. The United States Food and Drug Administration (FDA) approved the S-enantiomer of ketamine (esketamine), as the first antidepressant in a new class for treatment-resistant depression in 2019 (20). Emerging evidence has suggested that the use of ketamine as both a therapeutic and recreational substance is shifting. This article will highlight several key points regarding the usage of ketamine for physicians, policy makers, as well as patients and families.

Chronic Pain Management

Ketamine has been used clinically as early as the 1960s. Originally derived from phencyclidine (PCP), it can induce general anesthesia all while maintaining vital functions and reflexes in low doses. In low doses it can treat severe pain in postoperative patients. An understood safe dosage measures at a 0.15-0.3 mg/kg bolus or a 0.15-0.3 mg/kg/hr continuous infusion, whereas a 0.5 mg/kg dose has a higher rate of adverse effects and patient dissociation. Ketamine can be administered as needed for acute pain or it can be given continuously for chronic pain. Ketamine is unique in the way that a change in dosage changes the effects it has on the patient. At smaller doses not only can it be used as an analgesic but it can also be used as a refractory status epilepticus medication, a sedative, an anti-inflammatory, and an antidepressant. At high doses it shows adverse effects including hallucinations, depersonalization, and conceptual and mental disorganization. It can also worsen schizophrenia. Since adverse effects are mitigated by simply lowering dosages it has been a popular choice as there is a low risk of abuse when it is used to combat pain. This is in contrast to opioids which have been known to be addictive. It has been shown that patients who have been given ketamine need opioid medication less.[1]. It is also noted that ketamine is more effective at managing pain than a placebo, though the side effects include dizziness, nausea and vomiting, headache, and hallucinations. [3] Ketamine is rarely given as a solo drug. It can be more useful to use in combination as a sedative sparing agent and to reduce the possible patient misuse of opioid drugs.[7]

Anesthesia

When used as an anesthetic ketamine has shown its value by having amnesic properties in addition to maintaining body reflexes and stabilizing the respiratory and cardiovascular system.[1] It can be a part of non-operating room anesthesia (NORA) as it is very flexible in its administration through virtually any route. It is fast acting, hypnotic, carries minimal side effects, controls pain, and has no active metabolites. This makes it practical for use even in fussy children. The various routes of administration make it simpler when dealing with uncooperative patients or vein access difficulty. Venous access is not required for anesthesia as an intramuscular dose of 8-10 mg/kg or a nasal dose of 3-9 mg/kg can achieve the same results. Patients who are at risk of bronchospasms or malignant hyperthermia are safe to use ketamine. It also lends itself well to be combined with other sedatives, like benzodiazepine, to achieve anesthesia. Propofol is a popular choice to use in conjunction since it provides opposing properties which produce less hemodynamic instability, less vomiting, and recovery agitation. [2] Moreover, ketamine as a general anesthesia could promote postoperative cognitive function recovery, specifically S-ketamine. Normally a racemic mixture that can be obtained in pure form too, patients who were given specifically S-ketamine in their anesthesia reported an increased quality of recovery. Their physical comfort and emotional states were also reported to be higher. This is due to the increase in comfort and pain management. In addition, the patients who were given S-ketamine had a lower consumption of opioid [8]. It also can promote the recovery of cognitive function post operation. Propofol consumption is lowered as well.[4] as ketamine provides cardiovascular and respiratory stability, it is a choice anesthetic for the emergency department, status asthmaticus, trauma, burns, and with patients in shock.[8] to induce, an intravenous dose of 0.5-1 mg/kg is suggested with a maintenance dose at 0.5-3 mg/kg.[4]

Ketamine Receptors

Ketamine can thank its popularity to its NMDA receptors, which take part in synaptic transmission and plasticity. This plays a role in sedation, amnesia, and analgesia. It makes it a viable option for those who are in shock or hypotension since it excites sympathetic nerves and can relax the bronchi. Ketamine also interacts with opioid receptors, the monoamine system, AMPA receptors, and the cholinergic system. NMDA receptors are ionotropic glutamate receptors and are composed of three subunits: GluN1,

GluN2, and GluN3. Focusing on GluN2, it is composed of GluN2A, GluN2B, GluN2C, and GluN2D. GluN2A is the subunit responsible for synaptic plasticity and memory. GluN2B is the subunit responsible for central sensitization and chronic pain. When it comes to the opioid receptors S-ketamine proves to be at most four times more potent than R-ketamine when used as an analgesic because it binds to the μ and ***κ*** receptors like an opioid would.[2,5] Subsequently if using S-ketamine the dosage should be lowered, in comparison with R-ketamine, and as a result it is recommended S-ketamine should be combined with other sedatives.[2] With the AMPA receptors its purpose is to regulate the opening of the NMDA receptor channels.[5]

Cost Efficiency

Ketamine supply comes at low-cost to healthcare providers, with vials being priced at less than [6] depending on concentrated strength. [11] MThis combined with the long shelf life makes it a valuable drug. The liquid form of ketamine comes in vials that can keep over 95% relative strength even when left out in unfavorable environments. When left out in warm or fluctuating warm and hot temperatures, the drug can still be effective past six months.[6] This showcases its ability to be useful in sterile hospital settings and in the field, such as military locations or areas where there is little to no power, since it does not need to be refrigerated.

Ketamine for Convulsive Status Epilepticus

Ketamine has shown to act as an anticonvulsant and been used to treat status epilepticus since the 1990s,[8,10] The noncompetitive NMDA receptor antagonist aspect of it protects the hippocampal CAI neurons from seizure-induced neuronal necrosis.[8] Although more study is needed to determine the optimal dosing and timing of ketamine, it looks promising as a second-line or third-line treatment with midazolam or propofol for refractory status epilepticus.[8-10] There are various methods of drug administration. A loading dose could be anywhere from 0.5-5 mg/kg. A continuous intravenous infusion dosage could be from 0.05-10.5 mg/kg per hour and an enteral dose could range from 50-250 mg twice per day. The duration of ketamine treatment also varied ranging from 2 hours to 29 days after initial refractory status epilepticus diagnosis. Initial treatment could also be administered from 24 hours to 140 days after diagnosis.[10] Some of its positive assets are that it quickly penetrates the blood brain barrier and rapidly distributes into the sites of action, it targets a receptor related to excitotoxicity, and is upregulated during status epilepticus, refractory status epilepticus, and super refractory epilepticus. Its antiepileptic and neuroprotective effects are distinguished in animal models of status epilepticus so application in human epilepticus is innate. Its synergistic effects lend itself well to work with other antiseizure medications and it has sympathomimetic properties and vasopressor sparing effects. In addition, its availability is high as it is commonly held in hospitals for analgesia and anesthesia. Furthermore, it can be used in patients with traumatic brain injury and nontraumatic neurological diseases. Its bronchodilator property does not induce respiratory depression, preventing tracheal intubation, henceforth not needing mechanical ventilation. Along its positives is that it has immunomodulatory properties and effects on acute inflammation and stress-induced immune reactions.[8] Once the drug has taken course the therapeutic effect is achieved within a few hours. This effect is achieved with the administered dose exceeding 0.9 mg/kg per hour given at early onset of the episode. There is a possible recurrence after the cessation of the epilepticus.[10]

Pharmacology

With a single dose being 1-2 mg/kg over one minute, unconsciousness should be within 45 seconds and last for 10-15 minutes. The analgesia should last about 40 minutes and amnesia should last around 1-2 hours. Changes in EEG last 1-2 hours. When unconscious, alternating slow-delta and gamma oscillations are present as well as a lowered alpha power band and an increase in low-frequency and high-frequency activities. There is an increase in heart rate and systolic and diastolic blood pressure. The analgesic state and dysphoric reactions are mediated by opiate receptors. Additionally, it improves neuroinflammation.

Contraindications of ketamine are children younger than the age of 3 months and the schizophrenic.[8]

Ketamine for Depression

In 2019, esketamine, which is the S-enantiomer of ketamine was approved as an ancillary treatment specifically for treatment-resistant depression (TRD) in adults given only under medical supervision [12]. The S-enantiomer of ketamine is more potent at the NMDA receptor than the R, S racemic mixture of Ketamine creating antidepressant properties at a lower dose [12]. The decrease in dosage minimizes the potential adverse effects of ketamine which include dissociation, hypertension, tachycardia, and nausea [12]. Most recently in 2020, esketamine was also FDA approved for major depression disorder with acute suicidal ideation in adults [12]. Investigating ketamine further has the potential to transform our understanding of the mechanisms underlying mood disorders and the development of novel medicines in addition to introducing a fresh and beneficial treatment approach. Ketamine has also been studied as a novel add on therapy for Psychotic Treatment-Resistant Depression. It differs from traditional antidepressants and antipsychotics in that it has quick antidepressant effects and may be beneficial for people with psychosis and depression who have not responded to traditional treatments [13]. Ketamines NMDA antagonism makes it a unique pharmacotherapy for individuals not responding to existing treatments using the traditional receptors for psychiatric disorders.

Psychiatric Emergencies - for Psychosis but can also cause it.

Side effects

Ketamine, an NMDA receptor antagonist frequently used in anesthesia and increasingly for treatment-resistant depression, can lead to several side effects. Commonly reported adverse effects include dissociation, where patients may experience a sense of detachment from their body or surroundings, which can be distressing.[14] Additionally, ketamine use is associated with potential cognitive impairments and hallucinations, although these effects are generally transient.[15] Chronic use has raised concerns about urinary tract symptoms, such as cystitis, which can cause significant discomfort and may necessitate discontinuation of the drug.[16] Despite its therapeutic benefits, these side effects underscore the importance of careful monitoring and risk assessment in clinical use.

Addiction potential

Ketamine's potential for addiction is a topic of increasing concern and research. While primarily used as a dissociative anesthetic and for its therapeutic effects in treatment-resistant depression, ketamine's euphoric and hallucinogenic properties can lead to misuse and addiction.[17] Reports have shown that chronic use can result in tolerance, where users require higher doses to achieve the desired effects, and withdrawal symptoms upon cessation, indicating a potential for dependence.[18] The drug's availability and relatively low cost compared to other psychoactive substances further contribute to its abuse potential.[19] Given these risks, it is crucial to implement careful regulation and monitoring to prevent misuse and addiction while utilizing ketamine therapeutically.

Conclusion

Ketamine stands out as a versatile and valuable agent with substantial applications across pain management, anesthesia, and psychiatric treatment. Its distinct pharmacological properties, particularly its NMDA receptor antagonism, facilitate effective analgesia, reliable anesthesia, and promising antidepressant effects. When administered at appropriate dosages, ketamine generally maintains a favorable safety profile compared to opioids and other traditional therapies, thereby mitigating risks of dependency and abuse. The flexibility of ketamine's administration routes, combined with its cost-effectiveness and stability, underscores its utility in diverse clinical settings, from high-acuity emergency care to resource-limited environments. Its efficacy in managing refractory status epilepticus and its recent FDA approvals for treatment-resistant depression and acute suicidal ideation underscore its broad therapeutic potential and significance in modern medicine. Ongoing research will continue to refine ketamine's applications and enhance our understanding of its mechanisms. As new data emerges,

ketamine is well-positioned to revolutionize the treatment of complex medical conditions, offering novel solutions for patient care and contributing to improved clinical outcomes.

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