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Ketamine-The Confluence of Old and Recent Concepts

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Abstract

Not many drugs in anaesthesiology have gained so much attention as ketamine got for so many years. It has been used worldwide for the last five decades through various routes and for various indications. In its early year of its manufacture, it was considered a wonder or magic drug though the popularity declined with observation of so many side effects coming to the fore through various clinical trials. However, recently its non-anaesthetic properties and anaesthetic profile has re-kindled a newer interest in its pharmacological profile. Here we stand at a new juncture where a possible confluence of its old and recent utilities can make it a drug for future thus revolutionizing its clinical usage in many scenarios. The current narrative review aims to highlight these aspects through a short journey from its pharmacological profile to its older and recent indications.

Keywords: Dissociative anaesthesia; Ketamine; N-methyl-D-aspartate

Introduction

Ketamine was approved and first used clinically in 1970. It has been the time-tested drug in different clinical situations over last five decades. Its first published use was in pediatric ophthalmological procedures as an analgesic agent [1]. Ketamine is a solid pharmacological agent and is phencyclidine derivative. Although termed as dissociative anesthetic agent, but it has not dissociated itself from the anesthesiologist's shelf. It has been recommended as a core drug (a minimum medical need for a basic health system) by World Health Organization (WHO) on the basis of clinical trials, research statistics, various case reports and also from opinions of experts [2]. The current narrative review aims to highlight these aspects through a short journey from its pharmacological profile to its older and recent indications.

Search Strategies

The present review is compiled to highlight the understanding of the various old and evolving aspects of ketamine and its impact on anaesthesia practice. The measures adopted included extensive scrutiny of literary evidence from internet resources, journals and textbooks of medicine, anaesthesiology, pharmacology and intensive care. The strategiesincluded exploration of full text articles and abstracts from various search engines such as PubMed, Medscape, Scopus, Science Direct, Medline, Yahoo, Google Scholar and many others which included keywords like dissociative anaesthesia, Ketamine, N-methyl-D-aspartate, newer uses of ketamine, extra-clinical use of ketamine, recent concepts of ketamine.

A Short Beckoner of Pharmacological Profile of Ketamine

Bioavailability of ketamine via intravenous (iv), intramuscular (im), sublingual (SL), nasal, per rectal and per oral (PO) route is 99%, 93%, 30%, 45%, 30% and 20% respectively. Onset of action via im, subcutaneous and PO route is within 5, 15-30 and 30 minutes respectively. Time taken for peak plasma concentration with PO route is 30 minutes and 60 minutes with norketamine. Duration of action is 30 minutes to 2 hours with intramuscular route and 4-6 hours with PO route [3]. It can also be given via spinal route but concerns have been raised about its neurotoxicity.

Mechanism of action

Ketamine blocks N-methyl-D-aspartate (NMDA) type of receptors, inhibiting excitability of pain neurons. NMDA-glutamate receptor is associated with calcium channels of dorsal root neurons that transmit pain signals. Ketamine inhibits channel-related flux of calcium and sodium ions in presence of glutamate and glycine. It also inhibits neuronal hyperpolarisation-activated cationic currents, nicotinic acetyl-choline ion channels, act as agonist on delta and mu-opioid receptors, reduces cholinergic neuromodulation and increases release of dopamine and noradrenaline etc. ultimately affecting gene expression and protein regulation [4]. It dissociates thalamocortical system from limbic system [5]. Tone of pharyngeal and laryngeal muscles is preserved, thus decreasing risk of aspiration in case of vomiting.

Clinico-pharmacological profile

Ketamine acts as an anesthetic as well as an analgesic agent. It also acts as an anti-depressant, anti-inflammatory, neuro-protective and bronchodilator.

It should be used with caution in patients with history of psychiatric disorders, epilepsy, glaucoma, hypertension, heart failure, Ischemic heart disease, cerebrovascular accidents, acute intermittent porphyria and hyperthyroidism etc. Side effects include euphoria, dysphasia, psychomotor retardation, impaired memory and judgment, hallucinations, delirium, diplopia, blurred vision, nystagmus, hyper salivation etc.

Newer Evolving Concepts

Newer concepts of ketamine can be explained on the basis of its molecular pharmacology. It inhibits release of tumor necrosis factor-alpha (TNF-alpha), interleukin-6 and cytokines. Ketamine has one chiral center at the C-2 carbon and thus has two enantiomers ie. R and S enantiomers. S- ketamine is 3-4 times more active and also more potent analgesic agent than R- ketamine. R-ketamine is mostly used [6,7].

Epigenetic effects

Non-coding RNA molecules (such as miRNAs) have been considered as important regulators of neuronal functions. It has been observed that miRNA expression can be part of the antidepressant role in central nervous system [8]. Epigenetic mechanisms also influence gene expression. Ketamine alter histone deacetylase in nucleus accumbens, alleviate stress-induced depression, and suggest a role for Epigenetics in this situation. Epigenetic effects also account for the sustained therapeutic effects of ketamine.

Anti-inflammatory or immuno modulatory effects

Ketamine also act as unique homeostatic regulator of acute inflammatory reaction and stress-induced immune disturbances. It acts by inhibiting transcription activator protein-1 and nuclear factor (NF)-kB along with lowering of levels of interleukin (IL)-6, TNF-alpha, C-reactive protein etc. Thus it acts as an immunomodulator [9].

Impact of routes of administration

Although ketamine is used as anesthetic agent via multiple routes but even in sub anesthetic doses, it can provide analgesia. Its analgesic role in neuropathic and nociceptive pain is proven when given via multiple routes such as oral, transdermal etc. [10]. Intranasal ketamine can be used for breakthrough pain as ketamine 10%, which has also got the opioid-sparing effect. Onset of analgesia occurs within 5-10 minutes [11]. Ketamine has been used via s.c route in dose of 0.5 mg/kg for cesarean section either before or after the surgery [12].

Complex regional pain syndrome

Ketamine also plays important role in treatment of complex regional pain syndrome. Chronic pain is very severe due to complex sensory, motor, autonomic and dystrophic events. Ketamine alters central sensitization in chronic pain states [13].

Evolving use as an antidepressant

Recently ketamine has re-emerged as an off-label rapid-acting antidepressant in case of severe depression, resistant to other therapies [2]. It has been considered as one of the most exciting developments among antidepressant agents, which has been seen effective in bipolar affective disorders and suicidal ideation etc. According to several clinical observations, ketamine (in sub anesthetic doses) can be used alone or in combination with other drugs like amitriptyline for acute and chronic pain relief [14]. Various clinical studies have shown that ketamine in dose of 0.5 mg/kg IV has been used as rapid treatment for major depression, bipolar depression resistant to electroconvulsive therapy [14,15]. Incidence of hallucinations is reduced to less than 10% with concurrent use of midazolam [16]. Sub-anesthetic doses of ketamine are associated with impaired attention, memory and judgment, and it is also used as a pharmacological model for acute schizophrenia [17]. Chronic use of ketamine may be associated with neuropsychiatric, urinary tract and hepatic side effects, which may decline its use in chronic non cancer pain and cancer pain. Results of a large RCT are pending for use of oral racemic ketamine in cancer related neuropathic pain. Topical ketamine is also useful as oral rinse in radiation-induced mucositis [18]. Ketamine has been used as antidepressant in dose of 0.5 mg/kg with intravenous infusion over 40 minutes. Effect starts within 24 hours of intravenous infusion and can last upto 24 hours and can last up to 14 days. Several studies have been conducted to clearly know if it increases glutamate release or is primary NMDA block is the mechanism of action for its antidepressant effect of ketamine [19]. Ketamine in dose of 0.25-0.5 mg/kg has been used in operative deliveries to prevent shivering. It has been seen that prophylactic IV (intravenous) ketamine in dose of 0.25 mg/kg is as effective as 0.5 mg/kg in preventing shivering 12. Incidence of shivering is about 36-85% after spinal anesthesia. As we already know that spinal anesthesia impairs thermoregulation system by inhibiting vasoconstriction. Vasoconstriction plays an important role in temperature regulation. As heat gets distributed from core to peripheral compartment, sympathetic blockade due to spinal block inhibits vasoconstriction below the level of block, thus resulting in increased heat loss. Ketamine decreases core-to-peripheral redistribution of heat by direct central sympathetic stimulation and inhibition of norepinephrine uptake into postganglionic sympathetic nerve endings [20].

Analgesic in post tonsillectomy period

Ketamine has also been used as analgesic in post tonsillectomy period. As postoperative pain after this surgery is a significant problem in children. Ketamine inhibits early postoperative interleukin (IL-6) mediated inflammatory response. It is used via infilteration technique for pre-emptive and postoperative analgesia in the dose of 0.5 mg/kg, after induction of anesthesia and before surgical incision. Time to first demand of analgesic was longer in patients receiving ketamine. NMDA receptors present in peripheral somatic and visceral pain pathways play an important role in nociceptive, decreasing postoperative pain [21]. In another study by Honarmand et al. two different doses of ketamine have been used as 0.5 and 1 mg/kg body weight via peri tonsillar infilteration before surgical incision in adeno-tonsillectomy. Ketamine provided analgesia for 24 hours after surgery in children without side effects [22].

As a covering agent for opioid failure

In various studies, low dose ketamine (LDK) has been used for opioid failure, in patients who are at risk of respiratory depression, multiple opioid allergies, hypotension and chronic pain etc. Most of the physicians also believe that LDK has also been underused. It may reduce patient's perception of pain. In dose of 0.2 mg/kg IV, it provides analgesia with less psychological side effects. It has also been seen that chronic pain and opioid intolerance has been associated with up-regulation and activation of NMDA receptors in CNS. Ketamine also inhibits morphine metabolism, thus increasing duration of analgesia and it has got anti-inflammatory effects [23]. Sih et al. reviewed many studies of addition of ketamine to propofol (ketofol) during conscious sedation than patients' receiving propofol alone [24].

Emerging role in sepsis

Severe sepsis is the major cause of death in non-cardiac intensive care units (ICUs) with high mortality (30-50%). Along with primary damage to the organism, activation of leukocytes increases levels of cytokines, nitric oxide and reactive oxygen species. Cellular damage, platelet activation and endothelial dysfunction cause impairment of microcirculation and tissue perfusion, resulting in organ dysfunction. Ketamine can also affect septic course, may be due to immunosuppression via blocking the non-conventional receptors on immune cells. Ketamine affect several pathways in sepsis. Firstly, ketamine exerts its immunosuppressive effect on immune cells such as NK cell cytotoxic activity, neutrophil adhesion to endothelium and chemo tactic activity of neutrophils. Secondly, ketamine decreases Toll-like receptor expression, nuclear factor- kB activity, and Raf/Raf cascade. Thirdly, ketamine suppresses cytokines, superoxide and nitric oxide production and decreases mitochondrial membrane potential in macrophages. Finally, ketamine prevents alteration of immune function in patients early after a major surgery and increases survival in rats with sepsis. Since ketamine can cause arterial hypertension, tachycardia, myocardial depression, and dissociative effects, further clinical studies are needed to confirm safety and efficacy of intravenous ketamine in sepsis [25].

Procedural sedation

It has also been concluded from previous studies that ketamine in dose upto 4 mg/kg IV can be used for procedural sedation in children undergoing non-periorbital injuries and were evaluated for rise in intraocular pressure (IOP). It is used for procedural sedation as it provides amnesia, analgesia, anxiolysis and sedation without respiratory depression or fall in blood pressure. But further studies are needed to determine if ketamine can be used for procedural sedation if rise in IOP or globe injuries are concerns [26].

Role in sickle cell crisis

Patients with sickle cell crisis mostly present to emergency with complaints of musculoskeletal and abdominal pain. Various drugs like opioids etc. have been used. Low dose ketamine and midazolam combination has been used in a study. Initial bolus of ketamine in dose of 0.25 mg/kg, followed by infusion in dose of 0.2-0.25 mg/kg/hour was used along with midazolam. Bolus of 1 mg IV midazolam was followed by infusion in range of 0.5-1 mg/hour to reduce emergence delirium associated with use of ketamine. These patients have nociceptive, central and peripheral neuropathic pain. This combination significantly reduced daily morphine requirement. But further studies are needed to prove this fact [27].

Role in treatment of refractory status epilepticus

Status epilepticus is an acute and severe illness of central nervous system and prolonged status epilepticus can lead to brain damage and even death. As seizure duration increases more than 30 minutes, mortality rate is 19%. Ketamine alters glutamate metabolism, mainly in patients who exhibit poor response to benzodiazepines. During the seizure episode, number and activities of inactive GABA-A receptors on post synaptic membrane decrease along with increase in number and activities of glutamenergic NMDA receptors. Thus, efficacy of drugs with action on GABA ergic system such as diazepam, valproate, propofol and phenobarbitone decreases. In this case, efficacy of antiepileptic drugs can be increased with increase in their doses, but at the same time their cardiopulmonary side effects increase, thus limiting their use. Ketamine plays an important role in treatment of status epilepticus as it acts as a non-competitive NMDA receptor antagonist, preventing NMDA receptor-mediated glutamenergic neurotransmission. As it also blocks glutamate-mediated NMDA receptors-induced neurotoxicity, it also provides neuroprotection. Ketamine is highly fat soluble and low plasma protein binding rate, rapidly penetrates blood-brain-barrier, thus ketamine is given intravenously. According to one study, dose of oral ketamine is 1500-2000 mg/day for adults and 1.5 mg/kg/day, which is given as two separate doses in children. IV dose is 1.5 mg/kg followed by infusion rate is 2.75 mg/kg/hour for 4 days (0-24 days) is recommended in a study. But robust prospective studies are needed to investigate regimens, efficacy, and safety of ketamine for treatment of refractory status epilepticus [28].

Ketamine induced immunosuppression

Ketamine has been used in both human and animal models where its inhibitory action on functioning of lymphocytes, natural killer cells and neutrophils has been observed. It also suppresses chemo tactic activity and oxidant production by neutrophils. It also reduces TNF-alpha and nitric oxide production in lipopolysaccharide-activated macrophages. Both TNF- alpha and nitric oxide play an important role during inflammation and inhibition of these activities may affect macrophage-mediated immunity. Several in-vitro studies provide evidence to support the theory that ketamine exerts suppressive effects on macrophage function via inhibition of phagocytic activities, oxidative ability, and TNF-alpha, IL-1beta and IL-6mRNA syntheses occurring at transcriptional level. Tissue damage, anesthesia, postoperative pain and psychological stress affect immune system of the patient in perioperative period. Surgical trauma can induce a complex system of cytokines cascades with different effects on host as certain pro inflammatory cytokines are excessively stimulated and some cell-mediated immunity is suppressed. This excessive stimulation of pro inflammatory cytokines result into hypotension, shock and multi organ failure. Thus it is important suppress postoperative pain so as to reduce suppression of lymphocyte-mediated immune response and attenuate the pro inflammatory cytokines reaction to surgery. According to various studies ketamine exerts anti-inflammatory role by decreasing serum levels of IL-6 in postoperative period [29].

Chronic non-cancer pain

Sub-anesthetic doses of ketamine has been used in various types of non-cancer pain like complex regional pain syndrome type-I. It has been concluded f the results of 29 Randomized Controlled Trials (RCTs) that although ketamine provides adequate pain relief undesirable effects can limit its long term use.

Emerging newer undesirable side effects

Urinary tract symptoms in the form of urinary incontinence, hematuria and dysuria etc. are seen in patients who abuse ketamine. Risk is related to dose and frequency of use. Ketamine has got direct irritant effects on upper and lower urinary tract. Hepatobiliary dysfunction is seen in patients with abuse and therapeutic use of ketamine. Abnormalities of liver function tests, biliary duct dilation and pain abdomen are seen in these patients. Ketamine directly or its metabolites are toxic to liver. There are no reports of neuropsychiatric side effects with long term use of ketamine.

Conclusion

If we ignore and manage these older and emerging side effects by appropriate intervention, ketamine may possibly emerge again as one of the most important drug used in anaesthesiology and pain medicine. The emerging and evolving roles have shown a newer potential for its clinical usage. However, it is better to wait for all the ongoing clinical trials before we can label it a wonder drug in its true clinical sense.

References

1. Domino EF, Chodoff P, Coarsen G (1965). Pharmacological effects of C1-581, a new dissociative anesthetic in man. Clin Pharmacol Ther 6: 279-291.
2. Salvadore G, SinghJB (2013). Ketamine as a fast acting antidepressant: current knowledge and open questions. CNS NeurosciTher 19: 428-436.
3. Sinner B, Graf BM (2008). Ketamine. HandbExpPharmacol 182: 313-333.
4. Sleigh J, Harvey M, Voss L, Denny B (2014). Ketamine- More mechanisms of action than just NMDA blockade. Trends in Anaesthesia and Critical Care 4: 76-81.
5. Hirota K, Lambert DG (2011). Ketamine: new uses for an old drug? Br. J. Anaesth 107: 123-126.
6. Robson MJ, Elliott M, Seminerio MJ, Matsumoto RR (2012). Evaluation of sigma(σ) receptors in the antidepressant-like effects of ketaminein vitro and in vivo. Eur Neuropsychopharmacol 22: 308-317.
7. Preskorn SH (2012). Ketamine: the hopes and the hurdles. Biol Psychiatry 72: 522-523.
8. O'ConnerRM, Grenham S, Dinan TG, Cryan JF (2013). microRNAs as novel antidepressant targets: converging effects of ketamine and electroconvulsive shock therapy in the rat hippocampus. Int J Neuropsychopharmacol 16: 1885-1892.
9. Kock MD, Loix S, Lavand'homme P (2013). Ketamine and peripheral inflammation. CNS Neurosci Ther19: 403-410.
10. Kroneberg RH (2002). Ketamine as an analgesic: parenteral, oral, rectal, subcutaneous, transdermal and intranasal administration. JPain Palliat Care Pharmacother 16: 27-35.
11. Quinlan J (2012). The use of a subanesthetic infusion of intravenous ketamine to allow withdrawal of medically prescribed opioids in people with chronic pain, opioid tolerance and hyperalgesia: outcome at 6 months. Pain Med 13: 1524-1525.
12. Behaeen K, Soltanzadeh M, Nesioonpour S, Ebadi A, Olapour A, et al. (2014) Analgesic effect of low dose subcutaneous ketamine administration before and after cesarean section. Iran Red Crescent Med J 16: e15506.
13. Zur E (2014). Complex regional pain syndrometype I following trauma: a case-report. Int J Pharm Compd 18: 14-19.
14. Berman RM, Cappiello A, Anand A, Oren DA, Heninger GR, et al. (2000) Antidepressant effects of ketamine in depressed patients. Biol Psychiatry 47: 351-354.
15. DiazGranados N, Ibrahim LA, Brutsche NE, Ameli R, Henter ID, et al. (2010) Rapid resolution of suicidal ideation after a single infusion of an N-methyl-D-aspartate antagonist in patients with treatment-resistant major depressive disorder. J Clin Psychiatry 71: 1605-1611.
16. Sener S, Eken C, Schultz CH, Serinken M, Ozsarac M (2011). Ketamine with and without midazolam for emergency department sedation in adults: a randomized controlled trial. Ann Emerg Med 57: 109-114.
17. Mion G, Villevieille T (2013). Ketamine pharmacology: an update (pharmacodynamics and molecular aspects, recent findings). CNS NeurosciTher 19: 370-380.
18. Slatkin NE, Rhiner M (2003). Topical ketamine in the treatment of mucositis pain. Pain Med 4: 298-303.
19. Dutta A, McKie S, Deakin JF (2015). Ketamine and other potential glutamate antidepressants. Psychiatry Research 225: 1-13.
20. Kose EA, Honca M, Dal D, Akinci SB, Aypar U (2013). Prophylactic ketamine to prevent shivering in paturients undergoing Cesarean delivery during spinal anesthesia. JournalClinAnesth 25: 275-280.
21. Farmawy MS, Rashad MM (2014). Preemptive analgesia by peritonsillar ketamine versus ropivacaine for post-tonsillectomy pain in children. Egyptian Journal of Anaesthesia 30: 1-5.
22. Honarmand A, Safavi MR, Jamshidi M (2008). The preventative analgesic effect of preincisionalperitonsillar infiltration of two low doses of ketamine for postoperative pain relief in children following adenotonsillectomy. A randomized, double-blind, placebo-controlled study. PaediatrAnaesth 18: 508-514.
23. Richards JR, Rockford RE (2013). Low-dose ketamine analgesia: patient and physician experience in the ED. AmJEmerg Med 31: 390-394.
24. Sih K, Campbell SG, Tallon JM, Magee K, Zed PJ (2011). Ketamine in adult emergency medicine: controversies and recent advances. Ann Pharmacother 45: 1525-1534.
25. Tsao CM, Wu CC (2012). Modulating effects of ketamine on inflammatory response in sepsis. ActaAnaesthesiol Taiwan 50: 145-146.
26. Drayna PC, Estrada C, Wang W, Saville BR, Arnold DH (2012). Ketamine sedation is not associated with clinically meaningful elevation of intraocular pressure. Am JEmerg Med 30: 1215-1218.
27. Tawfic QA, Faris AS, Kausalya R (2014). The role of a low-dose ketamine-midazolam regimen in the management of severe painful crisis in patients with sickle cell disease. JPainSymptomManage 47: 334-340.
28. Fang Y, Wang X (2015). Ketamine for treatment of refractory status epilepticus. Seizure 30: 14-20.
29. Liu FL, Chen TL, Chen RM (2012). Mechanism of ketamine-induced immunosuppression. ActaAnaesthesiol Taiwan 50: 172-177.