Ketamine: Pharmacology Revisited

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Abstract: Ketamine, an old intravenous anesthetic, is a non-narcotic and non-barbiturate drug. It mainly works by non-competitive antagonist at the N-methyl-D-aspartate (NMDA) receptors. Ketamine has several properties of the ideal anesthetic agent. Therefore, its properties are interesting in various clinical settings, although it can produce the psychological adverse effects. This present short review aims to describe the pharmacology of ketamine.

Keywords: Ketamine, pharmacology, clinical.

INTRODUCTION

Ketamine is a neuroleptic anesthetic agent. It was introduced into clinical practice in 1958. It acts primarily as a noncompetitive N-methyl-d-aspartate (NMDA) receptor antagonist. Ketamine was originally used as a sole agent for anesthesia, inducing analgesia, amnesia, loss of consciousness, and immobility. However, it possesses some adverse psychological effects which occur during awakening from anesthesia. To date, the availability of S (+) ketamine has regenerated interest in its clinical use, because it has greater potency and fewer side effects. Low dose ketamine has also been used as a supplement to the regional anesthesia, for brief painful procedures, chronic pain syndrome and for opioid-resistant postoperative pain [1].

PHARMACOLOGY

Ketamine is a non-narcotic and non-barbiturate drug. It exists as a racemic compound containing equimolar amounts of S (+) ketamine and R (-) ketamine. The S (+) ketamine has a fourfold greater affinity for NMDA receptors then R (-) ketamine. In the clinical study, the recovery time is reduced with S (+) ketamine compared with the racemic mixture. The incidence of psychological side effects is the same with each at equal plasma concentrations. However, because a smaller dose of S (+) ketamine is required for anesthesia, there are less psychological side effects. Ketamine is freely water-soluble. Ketamine also has a highly lipid solubility and can cross the blood-brain barrier quicker. Its metabolism experiences by demethylation and hydroxylation. The metabolites are active, united and excreted in the urine. Norketamine has 20-30% of the activity of the ketamine.

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Ketamine also acts on the central nervous system. When ketamine used at higher dose, it has some local anesthetic properties. Its effects are mediated mainly at the NMDA receptors. Additionally, it reduces the presynaptic release of glutamate. The S (+) enantiomer has a three-to four-fold greater affinity for the NMDA receptor than the R (+) form. In subanesthetic dose, it was found to display analgesic properties because it binds to the mu and kappa opioid receptors [2, 3]. This binding effect with opioid receptors is complex [1]. However, naloxone can not antagonize these analgesic properties of ketamine [4]. Ketamine also implicates with the other receptors such as the monoaminergic, muscarinic and nicotinic receptors.

CARDIOVASCULAR EFFECTS

Ketamine is not a cardiovascular depressor drug. Therefore, it commonly uses in the hypovolemic patients and patients with hemodynamic instability especially for the trauma cases [5]. Additionally, ketamine conserves the cardiovascular function and has the least harmful effect on the hypoxic tissues when compared to the other anesthetic drugs [6]. Its cardiovascular effects are usually associated with tachycardia, hypertension and increased cardiac output. Pulmonary vascular resistance also tends to rise. As a result, ketamine should be avoided in the patients with coronary artery disease and hypertension. The increase of blood pressure initiates shortly after administration, and achieves a maximum effect within a few minutes. This effect usually returns to the baseline values within 15 min. Moreover, the hemodynamic alterations are not depended on the dose of administration. The exact mechanism of this mediated sympathetic response is still not known. However, ketamine also has a direct myocardial depressant effect. The undesirable cardiovascular effects can be reduced by administering ketamine as a continuous infusion technique. All physicians used this drug must

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be recognized and administered it carefully. Consequently, ketamine appears to be also has a peripheral action. This action works through the inhibition the intraneuronal uptake of catecholamines.

RESPIRATORY EFFECTS

Ketamine has minimal effect on central respiratory drive, although a transient decrease in ventilation can occur after bolus administration. The response to carbon dioxide is unaltered except the administration of a large dose. The airway reflexes and airway muscle tone are still conserved. Furthermore, ketamine is also a bronchial smooth muscle relaxant. It improves pulmonary compliance and is helpful in preventing bronchospasm. Therefore, it has been used to treat the patients with status asthmaticus unresponsive to the conventional therapy [7]. However, ketamine induces saliva and mucous secretions which can make some problems in the pediatric patients by causing laryngospasm and upper airway obstruction. Although airway reflexes, cough and gag reflexes are relatively intact, silent regurgitation and pulmonary aspiration can also happen. Anticholinergic drugs used before ketamine administration can reduce these secretions.

NEUROLOGICAL EFFECTS

Ketamine produces the dissociative anesthetic state that has been described as dissociative anesthesia. The electroencephalogram demonstrates a dominant theta activity with elimination of alpha rhythm. This anesthetic state is a cataleptic-like state of unresponsiveness with occasional coordinated but apparently unpurposeful movements of head, trunk and extremities. The patients' eyes remain open with a slow nystagmic gaze while the corneal and cough reflexes remain intact. Although, the patient has profound anesthesia, the hypertonus and occasional movements unrelated to painful stimuli are also observed. For epileptic effect, several previous studies had been demonstrated that the excitatory activity after ketamine administration had no clinical evidence of seizure. However, ketamine in subanesthetic dose has an analgesic property.

Moreover, ketamine increases cerebral blood flow, intracranial pressure with little effect on overall cerebral metabolic rate. The increase of intracranial pressure is generally related with increase of cerebral blood flow. Thus, its use in the patients with increased intracranial pressure or decreased intracranial compliance is not recommended. Additionally, ketamine has a neuroprotective effect in animals with cerebral damage [8]. The anticonvulsant activity of ketamine is due to the inhibition of the NMDA receptors [9].

One of the disadvantages of ketamime is the emergence reactions. These reactions have occurred in about 5-30% of the patients. These psychological manifestations after ketamine may differ in the severity and can be alterations in mood state and body image, floating sensations, dream-like states or illusions, delirium, confusion, excitement and unreasonable behavior. They usually occur in the first hour after administration and withdraw within 1-2 hours. These dreams and illusions usually disappear on full wakening. In addition, no residual psychological effects are observed. A higher incidence is associated with the factors such as increasing age but the least after the 65 years of age, female gender, the patients who normally dream, large dose and rapid intravenous administration. Ketamine may be associated with an exacerbation of psychosis in the patients with schizophrenia. Premedication with benzodiazepines appears to be an effective method in attenuating and treating these emergence reactions. Furthermore, the incidence is also reduced when used in combination with other sedative agents and general anesthetics [10, 11].

DOSAGE AND ROUTES OF ADMINISTRATION

The advantages of ketamine administration when compared with other anesthetic agents are that it can be administered through several different routes such as intravenous, intramuscular, oral, nasal, rectal, transmucosal and epidural routes. The dose depends on the route of administration and the preferred therapeutic effect [12]. The dose for induction of anesthesia is 0.5-2.0 mg/kg intravenous or 5-10 mg/kg intramuscular. In subanesthetic dose, 0.5-1.0 mg/kg intravenous or 0.5-5.0 mg/kg intramuscular is appropriate for sedation and analgesia. In addition, the dose for epidural administration is 20-30 mg/day and for caudal route is 0.5 mg/kg.

CONCLUSION

Ketamine, an old intravenous anesthetic, that it would carry the properties of the ideal anesthetic agent. It is a useful agent for induction of anesthesia, procedural sedation, and analgesia. Its properties are interesting in many clinical settings. However, it produces the psychomimetic side effects. The cardiorespiratory effects, several route of administration and low cost give ketamine the anesthetic agent of choice

for the developing countries. The incidence of adverse effects appears to be minimal at a subanesthetic dose. Additionally, a low dose ketamine may be a useful adjunct in the chronic pain patients. Ketamine is also becoming a valuable agent for emergency medicine.

REFERENCES

[1] Mion G, Villevieille T. Ketamine pharmacology: an update (pharmacodynamics and molecular aspects, recent findings). CNS Neuroscience & Therapeutics 2013; 19: 370-80. http://dx.doi.org/10.1111/cns.12099

[2] Amornyotin S, Aanpreung P, Prakanrattana U, Chalayonnavin W, Chatchawankitkul S, Srikureja W. Experience of intravenous sedation for pediatric gastrointestinal endoscopy in a large tertiary referral center in a developing country. Pediatric Anesthesia 2009; 19: 784-91. http://dx.doi.org/10.1111/j.1460-9592.2009.03063.x

[3] Amornyotin S. Pediatric sedation and analgesia in a developing country. Journal of Anesthesia and Clinical Research 2011; 2: S12: 001. DOI: 10.4172/2155-6148.S12-001.

[4] Amornyotin S. Sedative and analgesic drugs for gastrointestinal endoscopic procedure. Journal of Gastroenterology and Hepatology Research 2014; 3: 1133-44. DOI: 10.6051/j.issn.2224-3992.2014.04.397

[5] Amornyotin S, Chalayonnavin W, Kongphlay S. Assisted sedation for percutaneous endoscopic gastrostomy in sick patients in a developing country. Gastroenterology Insights 2010; 2 (e5): 17-20.

[6] Van der Linden P, Gilbart E, Engelman E, Schmartz D, de Rood M, Vincent JL. Comparison of halothane, isoflurane, alfentanil, and ketamine in experimental septic shock. Anesthesia & Analgesia 1990; 70: 608-17. http://dx.doi.org/10.1213/00000539-199006000-00006

[7] Heshmati F, Zeinali MB, Noroozinia H, Abbacivash R, Mahoori A. Use of ketamine in severe status asthmaticus in intensive care unit. http://www.ncbi.nlm.nih.gov/pubmed/17301376 Iranian Journal of Allergy, Asthma and Immunology 2003; 2: 175-80.

[8] Shapira Y, Lam AM, Eng CC, Laohaprasit V, Michel M. Therapeutic time window and dose response of the beneficial effects of ketamine in experimental head injury. Stroke 1994; 25: 1637-43. http://dx.doi.org/10.1161/01.STR.25.8.1637

[9] Ding Z, White PF. Anesthesia for electroconvulsive therapy. Anesthesia & Analgesia 2002; 94: 1351-64. http://dx.doi.org/10.1097/00000539-200205000-00057

[10] Amornyotin S, Chalayonnawin W, Kongphlay S. Clinical efficacy of the combination of propofol and ketamine (ketofol) for deep sedation for colonoscopy. Gut 2012; 61 (Suppl 2): A339-40. DOI:10.1136/gutjnl-2012-302514d.105

[11] Amornyotin S, Chalayonnawin W, Kongphlay S. Deep sedation for colonoscopy in overweight patients: a comparison between propofol alone versus propofol and ketamine. Journal of Physiological and Biomedical Sciences 2012; 25: 62.

[12] Jolly AS, Jain P, Sood J. Ketamine-current uses and future perspectives. Journal of Anaesthesiology Clinical Pharmacology 2007; 23: 169-81.

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