Journal of Experimental and Basic Medical Sciences 2022;3(3):227-231

Review

Antidepressant Effects of Ketamine

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ABSTRACT

Depression is recognized as a potentially fatal medical condition with far-reaching consequences. Antidepressants are used to treat depression. Ketamine is a short-acting anesthetic and pain reliever that is largely used in veterinary surgery. It is also employed in human medicine, albeit to a lesser extent. It is one of the safest anesthetics because it does not reduce breathing or heart rate. Ketamine has produced a lot of research in the last several years about its usefulness in treating specific mental health issues. But there's still a lot to understand about how ketamine works, how it's dosed, and what long-term consequences it can have on the body. Ketamine is an N-methyl-D-aspartic acid receptor pore blocker, which accounts for the majority of its activities except for the antidepressant effect, the mechanism of which is still being researched and debated. The effects of ketamine as an antidepressant on depression were compared and discussed in this review.

Keywords: Antidepressants, depression, ketamine, N-methyl-D-aspartic acid

Major depressive disorder affects how you feel, think, and behave and can cause a wide range of emotional and physical issues. It is a common condition that is considered a serious public health issue.[1] According to data from the United States, suicide is the tenth leading cause of death. Around the world, 300 million people are depressed, and 800,000 people have committed suicide. The national data from the United States show a definite increase in depression and, more importantly, untreated depression. Depression is the most significant risk factor for suicidal conduct, and these trends necessitate rapid intervention, particularly for adolescents and young adults, at both the clinical and public health levels. Expanding evidence-based efforts that encourage early intervention, prevention, and depression education is urgently required.[2]

Depression causes an increase in medical mortality and morbidity. It aggravates the symptoms of diseases such as stroke, delirium, myocardial infarction, chronic pain, and diabetes.[3] Depression became more common than before, with prevalence rates rising from 10.3% in 2015 to 15.5% in 2019 and 17.2% in 2020.[2]

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Cite this article as: Zerzevatcı C, Kılıçoğlu RB, Genç AS, Erbaş O. Antidepressant Effects of Ketamine. JEB Med Sci 2022;3(3):227-231.

doi: 10.5606/jebms.2022.1032

Received : November 25, 2022
Accepted : December 4, 2022
Published online : January 30, 2023

ANTIDEPRESSANTS

Until the 1930s, there was no effective treatment for depressive disorders. Almost all attempts during this period failed. There has been evidence of partial relief of symptoms such as distress and agitation in depressed patients using tinctura opii, first prescribed by Emil Kraepelin, but no positive effect on depressed mood or suicidal tendencies. A treatment for catatonia, a syndrome connected to schizophrenia, was also found in the 1930s. For the development of biological psychiatry, the realization that the experimental use of this treatment with psychogenic agents can induce catatonia has been a crucial turning point.[4]

Pharmacologists synthesized a series of phenothiazine amines after World War II that have a significant and long-lasting antihistamine effect. Promethazine was one of the most potent phenothiazine amine derivatives. Due to

promethazine's potential central nervous system effects, which have a sedative effect and a possible antipsychotic effect, many modified phenothiazine derivatives have been synthesized. Chlorpromazine, the first antipsychotic and the first antidepressant, was synthesized when chlorine was modified into the structure of promethazine.[5] Kuhn[6], a Swedish scientist, observed a substantial improvement in patients with psychiatric problems such as endogenous depression and mental and motor retardation treated with imipramine after one to six weeks of daily medication. As a result, the first tricyclic antidepressant with clinical evidence was discovered. As a consequence of their evaluation of patients whose tuberculosis depression could not be seen following the success of iproniazid, psychiatrists at Rockland State Hospital identified a new class of monoamine oxidase inhibitors.[7]

TREATMENT-RESISTANT DEPRESSION

Antidepressant medications have proven to be effective and beneficial for many people since their introduction. These medications have become regarded as first-line treatments for moderate to severe depression. Unfortunately, this treatment was insufficient for around one-third of the patients to achieve an effective result. Medication-resistant depression is defined as depression that does not respond to more than one first-line antidepressant treatment. Therapy-resistant depression has few treatment options and has become more common in recent years.[8]

Arylcyclohexylamine agents such as ketamine and phencyclidine (PCP) are known for their dissociative effects. In the 1950s, PCP was produced as a novel non-respiratory-depressant anesthetic. Although PCP has shown promise in preclinical studies, unacceptable side effects such as catatonia, psychosis, and agitation have been observed in humans.[9]

Ketamine offers similar anesthetic benefits to PCP derivatives, moreover, it has a more acceptable side-effect profile. Ketamine is most commonly used in the induction and maintenance of anesthesia and procedural sedation in the emergency room and other services. Ketamine has lately been used as a perioperative analgesic, especially in painful procedures and in opioid-dependent patients. Ketamine is also utilized in the prevention and treatment of chronic pain. Although the first studies of ketamine's antidepressant impact have been known for many years, its therapeutic use has only lately increased. Ketamine is used to treat acute depression and prevent suicide. Ketamine is a prototypical dissociator that also functions as an N-methyl-D-aspartic acid receptor (NMDAR) antagonist.[10]

KETAMINE

Ketamine was developed in 1963 at the Parke Davis Laboratory by a scientist called Calvin Stevens to replace PCP. Ketamine, which was utilized in veterinary medicine in Belgium during the years it was introduced, has been scientifically confirmed to have fewer hallucinogenic effects and shorter psychomimetic effects than PCP in 1964. Ketamine, which was approved by the Food and Drug Administration in 1970, was mostly employed in veterinary medicine, but it was also used to benefit from its anesthetic effects in youngsters and patients undergoing minor surgery. It is the only anesthetic that can be hypnotic, analgesic, and amnesic. For many years, it has been a favored agent in anesthetic applications. Ketamine is an NMDAR antagonist, a neurotoxic, environmental contaminant, and a xenobiotic with anesthetic properties.[11] It has high abuse potential and is illegally used as a psychoactive substance. Long-term ketamine usage can produce bladder and urethral inflammation and irritation, and comparable changes in the biliary tract have recently been observed, resulting in acute or chronic cholestatic liver damage that can mimic sclerosing cholangitis.[12] Ketamine belongs to the cyclohexanone class, in which one of the hydrogens in its two locations is substituted with a 2-chlorophenyl group and the other with a methylamino group. It belongs to cyclohexanone, a secondary amino compound, and is classified as belonging to the mono-chlorobenzene family.[13]

Pharmacological Effects of Ketamine

Dissociative anesthesia refers to the condition in which ketamine causes electrical dissociation between the cortical and limbic regions. The receptors to which it binds are not entirely understood, although they have an antagonistic effect on the central nervous system via NMDAR. S(+) ketamine and R(-) ketamine are the two enantiomers of ketamine. The racemic combination of these two enantiomers is the most economically desirable form. S(+) ketamine preparation has four times the affinity for NMDAR as R(+) ketamine. It binds to opioid receptors known as mu and kappa receptors. Furthermore, the anesthetic potency is three times that of a racemic mixture.[11] The frequency of adverse effects is the same for both enantiomers at equal plasma concentrations, but

since smaller doses of S(+) ketamine are required due to its higher potency, the single enantiomer formulation has fewer side effects and shorter recovery durations. Since the R(-) enantiomer has a larger effect on airway smooth muscle relaxation, the racemic mixture may be more suited for airway muscle safety. In the liver, ketamine is converted to its active metabolite, norketamine. Norketamine has the same impact as one-third of ketamine. Ketamine metabolites are eliminated by the kidneys after an elimination half-life of 2-3 hours.[14]

Ketamine Administration

Ketamine can be injected intravenously, intramuscularly, orally, rectally, subcutaneously, epidurally, or transnasally because it is soluble in water and fat. While it is 90% bioavailable in intravenous usage, it is just 16% in oral and rectal use. Plasma reaches its maximum concentration rate in 1-5 minutes of intravenous use and 15-30 minutes of oral intake. These variations are attributable to inadequate gastrointestinal absorption and the first-pass action on the liver. The analgesic efficacy of oral ketamine is explained by the fact that norketamine levels are three times higher after oral administration than after intravenous treatment.[15] Ketamine is also given intravenously, either alone or in combination with other local anesthetics. The medulla spinalis binds to NMDAR in the posterior horn and demonstrates an analgesic effect for a long period with a single application. The racemic combination of ketamine is available in three sorts of concentrations; 10 mg/ml, 50 mg/ml, and 100 mg/ml.[16]

Clinical Effects of Ketamine

Pharyngeal and laryngeal reflexes are frequently intact under ketamine anesthesia, and the airway is usually protected. Some signals cause laryngeal spasms, which can be alleviated by simple airway manipulations. Breathing usually persists as a result of the stagnant administration. Ketamine can cause sympathomimetic action since it decreases catecholamine reuptake. Therefore, it can modestly or moderately increase heart rate, blood pressure, stroke volume of the heart, and myocardial oxygen demand.[17] Ketamine induces dissociative anesthesia, resulting in patients' eyelids opening during anesthesia and operation. Reflex motor movements are occasionally seen. Patients may awaken agitated as a result of hallucinations during recovery. Women are more likely to have hallucinations as a result of high-dose usage and fast intravenous delivery. Premedication with benzodiazepines is frequently used to avoid hallucinations.[18] Ketamine is increasingly being utilized to treat intraoperative, acute, and chronic pain. Both intravenous and oral doses provide analgesic relief. Since norketamine has no hallucinogenic effect, oral administration has fewer negative effects. Ketamine has been avoided in patients with head injuries for many years due to concerns that it raises intracranial pressure. However, unlike other sedatives, it has recently been shown that it does not inhibit the hemodynamic impact, therefore, it enhances cerebral perfusion while having no significant effect on intracranial pressure.[19]

KETAMINE AND DEPRESSION

Depression is a serious mental disorder that has a significant negative impact on one's quality of life. Throughout their lives, 10-30% of women and 7-15% of males will experience clinically and biologically diverse depression. Depression is a condition with a high morbidity and death rate, as well as substantial economic and social ramifications. Serotonin and/or noradrenaline reuptake inhibitors are now frequently utilized to treat depressive symptoms. However, late commencement of effectiveness periods and low reabsorption rates are viewed as severe drawbacks in these medications.[20] As a result of these issues, there is an urgent need for an antidepressant medication that is both quick and effective. For a long time, studies have focused on the late start of antidepressant effects, the high frequency of side effects, and the pathophysiology of mood disorders. In addition to the monoaminergic system, the glutamatergic system, which is another neurotransmitter route, has lately received a lot of attention. According to the findings of the studies, the glutamatergic system may be a promising target for the quick response to therapy for the medications that are being developed for the treatment of depression. Ketamine has a strong, non-competitive antagonistic effect on NMDAR, which is an ionotropic receptor in the glutamatergic system. Glutamate is the primary mediator for excitatory synaptic transmission in the brain of mammals and is known for having a significant active role in synaptic density, learning, and memory. The glutamatergic system plays a significant role in the pathophysiology of major depression and the mechanism of antidepressant medication, and this topic has been the subject of much research. N-methyl-D-aspartic acid receptor, in particular, has been linked to depression and the effects of antidepressant medications.[21] Furthermore, antidepressants that have long been used in chronic therapy have been demonstrated

to influence NMDAR function. As a result of the outcomes of these investigations, it is believed that the mechanism of NMDAR antagonism may be a viable therapy option for depression. Ketamine has been utilized as a successful treatment option for millions of patients over the last 40 years due to its consistent anesthetic profile. Ketamine, as an NMDAR antagonist, has been proven in recent years to offer rapid-onset and transient antidepressant benefits in treatment-resistant depression patients.[22]

Duration of the Antidepressant Effect of Ketamine

Ketamine's antidepressant impact generally lasted 1-2 weeks following a single dosage in tests. Later developments were conducted to verify that this interval is prolonged. A second ketamine dosage has been tried in numerous case reports in case of recurrence in patients who reacted to the initial ketamine treatment. Dose delivery intervals range from 10 days to six months. In two situations, the second dose had a poorer reaction than the first. In a case series of two patients, the first was administered 0.5 mg/kg ketamine in six sessions every other day, whereas the other was given ketamine on days one and seven and a placebo on the other days. After a few days, both patients showed a significant response to therapy. However, although the patient who received two doses of ketamine experienced recurrence on the 25th day, the other patient experienced it on the 40th day.[23,24]

Depression is a major issue all over the world. The development of new antidepressants has lately stalled. Traditional antidepressant drugs are still the primary therapy choice. A considerable number of individuals with serious depressive disorders are unable to achieve clinical response with conventional therapy. In this instance, new therapies and interventional methods are necessary. Ketamine was shown to be successful, with 40% to 60% of individuals responding after ketamine infusion matching clinical criteria following antidepressant therapy. Ketamine is being studied for its acute antidepressant effects in individuals who have not responded to conventional therapy. The antidepressant effect of ketamine is related to NMDAR antagonism, while other NMDAR antagonist drugs have not been proven to have significant antidepressant effects. New preclinical findings suggest that ketamine's antidepressant effects are related to NMDAR antagonism and regulation.[8,25]

In conclusion, although ketamine has long been known for its effects, it has not been used to its full potential. However, ketamine and its metabolites may be quite beneficial in treatment-resistant depression if the effectiveness of other antidepressant medicines is insufficient. Ketamine has been found to have fewer negative effects than similarly related compounds, and its usage may be favored more frequently.

Declaration of conflicting interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding

The authors received no financial support for the research and/or authorship of this article.

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