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REVIEW

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Ketamine-An Update on Its Clinical Uses and Abuses

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SUMMARY

This review highlights the recent clinical research that supports the therapeutic utility of ketamine as a multifaceted drug. After long-term use as a dissociative anesthetic, it has re-emerged as a useful agent for ameliorating pain, asthmaticus, and depression. In addition, it is also a substance of abuse. Chronic ketamine abuse over prolonged periods (weeks, months, and years) can produce toxicity to the gastrointestinal and urinary tract. In this review, we described the recent progress on its clinical uses and abuses.

Introduction

Ketamine, originally named "CI581," is a phencyclidine derivative. It has a molecular weight of 238 Da and a pKa of 7.5 [1]. There are two isomers: *S* (+) eutomer ketamine and R (−) ketamine [2]. S eutomer has several advantages over the R (−) isomer. The S (+) isomer, an active enantiomer [3], has a 4-fold greater affinity for the NMDA receptor, twice the analgesic potency, and fewer psychomimetic effects than the *R* (−) isomer. Commercially available ketamine is a chiral compound consisting of a mixture of both two isomers [4].

The most efficient route of administration is intravenous injection (bioavailability: 99%). While oral bioavailability of ketamine is only 16% [5]. The onset of action is rapid, and peak plasma concentrations are seen within 60 seconds of administration. The duration of action after a single bolus injection is 10–15 min and distribution half-life is 7–11 min [6]. Based on these properties, it is suitable as a parenterally administered anesthetic for children patients [7]. In addition to producing anesthesia in emergency department and operating theater settings [8], ketamine has shown significant effects on treating depression. The desired action represents an efficacious approach to amelioration of major depression, treatment-resistant depression, bipolar affective disorder, and suicidal ideation [9–13]. Furthermore, numerous studies prove that ketamine can be used alone and in combination with other drugs for pain relief in patients experiencing various surgeries and traumatic injuries [14–16]. More recently, the addition of ketamine to the standard treatment regimen of severe asthma has shown to improve outcome and alleviate the need for mechanical ventilation, suggesting ketamine might be a novel and rapid-acting drug in the treatment of patients with asthmaticus [17,18].

However, the dose- and duration-related side effects of ketamine are usually reported, such as psychotomimetic effects, increases in blood pressure and heart rate [19,20]. Being a strong psycho-stimulant, ketamine can also be the source of abuse, which could result in schizophrenia-like cognitive impairments and multiorgan dysfunction [21–23].

This review will focus on two important aspects of ketamine: its clinical uses as a potential medication and the severe problems related to its abuses.

Major Depression

Successful treatment of depressive disorders remains as challenging today as it was nearly 100 years ago. Current approaches to major depression are highly unsatisfactory. In 2000, the first placebo-controlled, double-blinded trial demonstrated that ketamine has therapeutic effects in major depression [24]. After that, numerous RCT studies focusing on the effects of ketamine on major depressive disorder suggested a significant and rapid improvement in depressive symptoms after a single ketamine infusion [25,26]. The rapid-acting antidepressant could maintain its therapeutic effects for about 3–7 days [27]. Given that the effects of a single dose of ketamine were transient, another study

assessed the efficacy of repeated doses for depressive patients. A total of ten patients participated in the research and received repeated ketamine treatment over the course of 6 days (six infusions). The response criterion was met by nine patients after the sixth infusions. Postketamine, eight of nine patients relapsed, on average, 19 days after the sixth infusion. One patient remained significant improvement in depressive symptoms for more than 3 months [28]. These findings suggested feasibility of both single and repeated dose infusion ketamine for the treatment of major depression.

Although the oral bioavailability of ketamine is relatively low, there are still some researches attempt to study its antidepression effects as oral administration is the simplest way to implement, which may be especially relevant to maintained treatment. A small case report with two patients given a single, oral ketamine for depression demonstrated rapid and modestly sustained symptom relief of depression [29]. Recently, a larger open-labeled trial with 14 patients demonstrated there was significant improvement in depressive symptoms after these patients received daily oral dose of ketamine over a period of 28 days [30]. Further investigation with randomized, controlled clinical trial is necessary to firmly establish the oral efficacy of ketamine for the treatment of depression.

Evidence is accumulating that excessive glutamate levels play a major role in depressive pathophysiology and, consequentially, glutamate antagonists could prove fruitful [31,32]. Ketamine can be classified as a nonselective, noncompetitive, high-affinity NMDAR antagonist [33]. Mechanistic studies suggested that ketamine inhibition of NMDA receptors leads to glutamate release and the activation of other glutamate receptors [34].

Low BDNF levels are associated with major depressive disorder, and ketamine has been found to increase BDNF levels via stimulation of a-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor, which is a glutamate receptor [35,36]. The use of conditional knockout mice has suggested that BDNF is required for the antidepressive-like effect of ketamine [37]. In addition to AMPAR signaling, other assert rapid mood elevation is mediated by fast inhibition of nitric oxide synthesis as the NMDA-R is an ionotropic–glutamate receptor subtype that activates nitric oxide synthase (NOS). The delayed and sustained antidepressant effects of ketamine were mediated by NMDA-R/PSD-95/nNOS pathway [38].

Furthermore, numerous studies revealed ketamine possibly exerts its antidepressant action through interaction with 5-HT_{2A} receptors, which are known to play an important role in the pathogenesis of major depressive disorders [39,40]. It could either inhibit the 5-HT transporter (SERT) in a dose-dependent manner or increase extracellular levels of 5-HT and 5-HT tissue contents in the brain of rodents [41,42].

Suicidal Ideation

Suicidal ideation is a potentially life-threatening indication for medical emergency services [43]. Rapid and effective interventions are needed due to the relationship between suicidal ideation and attempts/death. Numerous studies showed that a single subanesthetic dose (0.5 mg/kg over 40 min) of ketamine could resulted in reductions in suicidal ideation [44]. In patients with depressive disorder, suicidal ideation scores decreased significantly within 40 min of a ketamine infusion and remained improved for up to 4 h postinfusion. Price et al. [45] found out in addition to a single subanesthetic dose of intravenous ketamine, thrice-weekly ketamine infusions over a 12-day period has rapid beneficial effects on suicidal cognition as well, and these antisuicidal effects remained significant for several weeks.

Proposed mechanisms of action of ketamine were as follows: first, ketamine reduces suicidal thoughts through its impact on improving depression symptoms as ketamine has been shown to reduce depression [46]. In support of this perspective, several randomized clinical trials revealed that in adults, reduction in suicide ideation and attempts occurred through a reduction in depressive symptoms. In all age groups, severity of depression improved with medication and was significantly related to suicide ideation or behavior. A randomized controlled trial in treatment-resistant depression suggested that improvements in depressive symptoms mediated the reductions in suicide ideation after ketamine infusion [12]. Second, ketamine could reduce the anxiety, and reductions in anxiety symptoms mediated the reductions in suicidal thoughts after infusion [47]. In fact, elevated anxiety and a history of anxiety disorder in the context of an affective disorder have been associated with imminent and long-term risk of suicide behavior. A total of 133 patients with treatment-resistant depression received a single subanesthetic infusion of ketamine, and following results revealed that improvements in suicidal ideation after infusion are related to improvements in anxiety [44].

Third, ketamine had an impact on increased wish to live and decreased wish to die, which were two cognitive aspects of suicide ideation. It is worth mentioning that while changes in suicidal ideation and depression were significantly correlated, the depression symptoms only accounted for about 19% of the suicidal ideation. Many individuals think about attempt and die by suicide outside the context of a depressive episode [48]. Ballard et al. [44] found that the effect of ketamine on suicidal thoughts was still significant when controlling for depressive symptoms simultaneously. These effects might be related to enhanced neuroplasticity after ketamine infusion. Patients with robust improvements in depressive symptoms after ketamine infusion exhibited increased cortical excitability within this antidepressant response window.

Treatment-Resistant Depression

Until now, the definition of treatment-resistant depression (TRD) has been subject to debate; however, the general consensus is that for a diagnosis of TRD, treatment with antidepressant from different pharmacological classes has failed to produce a response. It consists of a substantial number of patients with major depressive disorder (MDD) and bipolar depression (BD) who do not respond to current antidepressant therapy [49]. Treatment failure in depressive patients usually associated with considerable morbidity and the risk of suicidal behavior. Thus, a rapid antidepressant response in these patients is needed. Neurocognitive performance such as attention and memory improved significantly after completion of six ketamine infusions in TRD [50]. For individuals with major depressive disorder, response rates to ketamine at 4 h and 24 h were 56% and 71%, respectively, while for patients with bipolar depression, response rates at 4 h, and 24 h were 61% and

41%, respectively [51]. Higher body mass index and family history of an alcohol use disorder in a first-degree relative are found to predict the ketamine response in patients with TRD [52]. A plasma metabolomics study in 22 BD patients demonstrated that the greater plasma concentration of D-serine (D-Ser) was a contributing factor to the antidepressant response after ketamine infusion [53].

Bipolar Depression

Bipolar (affective) depression, originally called manic depressive illness, is one of the most challenging psychiatric disorders to manage [54]. It is characterized by recurrent episodes of elevated mood and depression, together with changes in activity levels [55]. More than 6% die through suicide in the two decades after diagnosis [56]. Treatment is guided by whether mania or depression predominates. A rapid antidepressant effect of ketamine infusion maintaining for 2 weeks was observed in a considerable proportion of patients with bipolar depression [57]. Administration of ketamine sublingually every 2–3 days or weekly to patients with bipolar depression demonstrated rapid and robust effects on mood in 77% of cases [58]. In addition to adult patients, children with bipolar disorder also showed significant improvement in mood and behavioral symptoms after intranasal ketamine administration [59]. The reasonable explanation for the efficacy of ketamine in bipolar depression was related to NMDA signaling. It has been reported that an increasing level of glutamate, a ligand for NMDA receptor, was found in cortex of bipolar depressive patients [60]. Ketamine, a NMDA receptor antagonist, could exert its therapeutic effects by inhibiting the excessive activation of NMDA receptor. In a double-blind, randomized, cross-over study, Twenty-one subjects with BD currently in a depressed state underwent [(18) F]-fluorodeoxyglucose (FDG) positron emission tomography (PET) imaging after receiving a placebo infusion as well as after receiving a ketamine infusion [61]. Regional metabolic rate of glucose (rMRGlu) in regions of interest was measured. The following results revealed that ketamine administration altered glucose metabolism in areas known to be involved in mood disorders; these alterations may partially underlie ketamine's mechanism of action.

Asthmaticus Attacks

Status asthmaticus is a unique and dynamic condition requiring rapid and aggressive intervention. Patients with asthma are predisposed for developing acute exacerbations, which may lead to respiratory failure [62]. Decision of invasive ventilation should not be embarked upon because of its associated complications like air-leak syndromes. Numerous studies revealed that ketamine was a useful drug in the intensive treatment of status asthmaticus and adding it to the standard treatment regime could avoid the need of mechanical ventilation [33]. The first example using ketamine successfully to avoid the need for mechanical ventilation was described by Strube and Hallam [63] A 13-year-old girl with severe asthma regained consciousness 30 min after continuous intravenous infusion of ketamine. For children experiencing severe asthma exacerbations, intravenous ketamine led to prompt improvement and avoid the need for mechanical ventilation [64]. Even in mechanically ventilated patients with refractory bronchospasm, continuous infusion of ketamine significantly improves gas exchange and dynamic compliance of the chest [65–67]. Several mechanisms of action have been proposed to explain this effect.

First, NMDA receptors exist in the airway, and their activation seems to be linked to the release actions of sensory neuropeptides resulting in increased airway tone. The bronchodilator ketamine mediated the relax of tracheal smooth muscle by blocking the NMDA receptor [68].

Second, increased nitric oxide levels have been proved to mediate bronchospasm. Ketamine inhibits overexpression of mRNA and protein of induced nitric oxide synthetase and reduces the production of nitric oxide in pulmonary tissues [69].

Third, release of inflammatory mediators played an important role in airway hyperreactivity in acute asthma. Ketamine can suppress inflammatory cytokine production and interfere with the recruitment of macrophages [70]. Thus, it is a potent antiinflammatory agent useful in acute asthma.

Lastly, ketamine increases synaptic catecholamine levels by blocking the reuptake of norepinephrine into presynaptic sympathetic neurons [71]. These endogenous catecholamines act on $\beta 2$ receptors and lead to bronchodilation. It has been shown that increase in free norepinephrine parallels the peak bronchodilatory effect of ketamine, and this effect can be diminished by β-adrenergic blockade.

Pain

Postoperative pain is one of the most important reasons for the patients' maladies after surgery and can require intensive pain management for several days. Arthroscopic shoulder surgery (ASS) is associated with moderate to severe postoperative pain, which can require intensive pain management. The gold standard for postoperative analgesia following ASS is continuous interscalene nerve block (CISB), which provides better analgesia than the other modalities [72]. However, a single-injection nerve block is simple but has a limited duration. An effective adjuvant that prolongs the duration of a single-injection nerve block may be a good alternative to a continuous nerve block.

Activation of N-methyl-D-aspartate (NMDA) receptor played an important role in the development of perioperative nociception-related neural sensitization, hypersensitivity, and opioid tolerance [73,74]. Therefore, ketamine, a noncompetitive NMDA receptor antagonist, has analgesic, antiinflammatory, and antihyperalgesic effects. Combining a femoral nerve block with small-dose ketamine could reduce the postoperative pain and speed rehabilitation after total knee arthroplasty [75]. Very-low-dose ketamine (0.05 mg/kg/h) has shown better early postoperative pain relief in patients undergoing open thoracotomy. However, studies conducted in abdominal hysterectomy and open colorectal surgery did not confirm such relief [76,77].

The controversial results may be related to the infusion period of ketamine. Treatment with ketamine during the preoperative and intraoperative periods may be insufficient to provide pain relief as peripheral tissue injury and the inflammatory response to the damaged tissue during an operation induces sensitization and contributed to postoperative pain [78]. Thus to obtain the opti-

mum of analgesic effects, ketamine infusion should start before the surgery and last postoperation.

For children, severe pain after surgery is the most common complaint. Proper pain relief after surgery is meaningful, which could increase their compliance and facilitate the recovery. Especially in children with tonsillectomy, difficulty swallowing, mainly caused by severe pain, could result in decreased food intake and subsequent dehydration. Using ketamine preemptively as an analgesic adjuvant has shown the effects on postoperative pain. Under many circumstances, the opioids injections are most commonly used to control the pediatric pain [79]. However, systemic opioids may cause respiratory depression. It has been found that intravenous ketamine is effective in reducing total opioid requirements in many procedures. Combination opioid with ketamine could significantly decrease the dose of opioid in certain surgeries and thus cause less respiratory problems in children sensitive to opioid.

Abuse

Ketamine abuse is being increasingly reported worldwide. It can produce a dissociative state and hallucinations, making it a favorite recreational agent among drug addicts. Although death from acute direct toxicity is rare, its chronic abuse can produce toxicity to the gastrointestinal and urinary tract [80,81]. Furthermore, it can alter numerous functions in the brain including color perception, memory, attention, cognition, reaction time, and sense of time and can produce psychological addiction [82]. In the following chapter, we will discuss these severe problems related to its abuse in detail.

Toxicity to the Gastrointestinal Tract

Gastrointestinal changes in ketamine abusers include epigastric pain, hepatic dysfunction, and impaired gallbladder activity. A retrospective study conducted by Poon et al. [83] revealed that ketamine abusers frequently presented with upper gastrointestinal symptoms, the commonest of which is epigastric pain. The possible cause for epigastric pain is biliary tract abnormality. Computed tomography and endoscopic retrograde cholangiopancreatogram showed a dilated biliary system in patients who had a history of ketamine abuse for more than 1 year [84]. The diameter of the bile duct is up to 9 mm, which was suggestive of a choledochal cyst. The biliary dilation and subsequent cholestasis usually mimic the symptoms of obstructive jaundice in the absence of an obstructing lesion [85]. Likely explanation for this phenomenon is that ketamine could cause smooth muscle relaxation directly through inhibiting the activation of NMDA receptor. Liver injury is another common complication among chronic abusers of ketamine. In a cross-sectional survey of 297 consecutive chronic abusers, the prevalence of liver injury was 9.8% and all cases are cholestatic related [86].

Toxicity to the Urinary Tract

Severe lower urinary tracts symptoms (LUTS), including urinary frequency, urgency, and dysuria, are commonly found in active ketamine users [87]. The irritative urinary symptoms are a sign of reduced functional bladder capacity. Several pathophysiological mechanisms, including epithelial dysfunction, mast-cell activation, and neurogenic inflammation have been proposed to explain symptoms [88]. Patients suffering from these irritative urinary symptoms can develop interstitial cystitis [89]. After cessation of ketamine use, the symptoms in these patients improved. Bladder biopsies showed denudation of urothelium and infiltration of submucosa with lymphocytes and eosinophils with no increase in mast cells [90]. Although the association between the ketamine abuse and the development of cystitis is well established, the exact mechanism remains unknown. Animal studies demonstrated that ketamine disrupted the proliferation of bladder epithelial cells, resulting in defected bladder epithelial barrier and subsequent leakage of urinary potassium, which directly causes a stress response in the bladder and provokes cystitis [88]. There is concern that possible irreversible secondary renal damage, including hydronephrosis and deranged renal function, may also be a complication [91]. A retrospective study demonstrated that in patients with ketamine-induced uropathy, 44.4% were diagnosed with hydronephrosis [92]. Another study investigated clinical symptoms in young abusers of street ketamine (regular recreational abusers of street ketamine, for its hallucinogenic effects) in Hong Kong. Of the 59 patients, thirty patients (51%) had unilateral or bilateral hydronephrosis on renal ultrasonography, and four (7%) showed features suggestive of papillary necrosis on radiological imaging [93]. Eight patients had a raised serum creatinine level. These severe complications such as hydronephrosis and renal dysfunction might finally render patients to depend on dialysis, suggesting ketamine abuse is not only a drug problem, but might be associated with a serious urological condition causing a significant burden to healthcare resources.

Conclusion

Ketamine is an example of how an existing drug can be readapted for multiple uses including treatment of depression and asthmaticus. The mechanisms of ketamine effects are mainly related to its inhibition to NMDA receptor pathway. It has the potential to become the first-line antidepression medication, especially to the refractory and major depression. It alleviates the need for mechanical ventilation when administered in combination with other drugs in patients with severe asthma. Besides, it's also an effective adjuvant that prolongs the duration of a single-injection nerve block in pain management and a safe choice for children to alleviate surgery-related pain. However, it is a dissociative anesthetic and substance of abuse, chronic ketamine abuse can produce toxicity to the gastrointestinal and urinary tract.

Conflict of Interest

The authors declare no conflict of interest.

Disclosure

Neither the entire article nor any part of its content has been published or is under consideration for publication elsewhere. There are no companies that may have a financial interest in the information contained in the manuscript.

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