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Review

KETAMINE - UNDRAWN LINES BETWEEN MEDICAL AND RECREATIONAL USE - IMPLICATIONS FOR CLINICAL PRACTICE

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SUMMARY

Ketamine, synthesized in 1962, approved in 1970, is considered safe for use in controlled conditions, mainly as an anesthetic, especially in pediatric populations and in people suffering from pulmonary diseases, as well as in emergency departments and in war situations. Dissociative states (derealization and depersonalization) produced by ketamine made it a popular recreational drug, which led to increased regulation in most countries. Intravenous application of ketamine has shown rapid, although transitory antidepressant and antisuicidal effects in patients with unipolar and bipolar depression. Esketamine, the S(+) enantiomer of ketamine, with better pharmacodynamic selectivity, has just been approved for treatment-resistant major depressive disorder, in the form of a nasal spray. Presently, the high cost of the spray not only limits its widespread use, but also makes it less prone to abuse and diversion. Additional measures are needed to hinder it from becoming a new "street drug".

Key words: *ketamine – esketamine – antidepressant - ketamine abuse*

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INTRODUCTION

Ketamine was synthesized in 1962 by Calvin Lee Stevens, a professor of Chemistry at Wayne State University, while looking for a short-acting derivative of phencyclidine (PCP), with a more favorable tolerability profile, such as lower risk of hypertension and post-operative delirium. In 1966, Corssen and Domino published the first clinical study of ketamine as a "dissociative anesthetic". Having been approved by FDA in 1970, ketamine received wide use as an anesthetic during the Vietnam War and it has remained one of the most utilized anesthetics ever since. Additionally, it is employed for pain management in emergency medicine, as an alternative to opioids. During the 1970ies, it was also tried as an adjunct for psychotherapy in Latin America, with limited success (Khorramzadeh & Lotfy 1973). In recent times, racemic ketamine and, more frequently, its (S)+ enantiomer (esketamine) have been used in acute treatment of depression, due to their fast-acting antidepressant, antisuicidal and antianhedonic effects. We are going to discuss ketamine's action as a novel antidepressant, in light of its potential side effects and its possible diversion as a recreational drug.

PHARMACOLOGY

Ketamine is considered a "dirty drug" modulating various biological targets. Its full mechanism of action is not fully understood. Ketamine's proposed mode of action is via open-channel uncompetitive antagonism (K_i=0.25–0.66 μM) of the N-methyl-D-aspartate (NMDA) receptors, which are ionotropic glutamate receptors (Tyler et al. 2017). It binds to dizocilpine (MK-801) site of the NMDA receptor (which is also known as the PCP site of this receptor).

Arketamine and esketamine bind to this site with unequal affinities, with esketamine showing roughly 3 to 4 fold stronger affinity for this receptor than arketamine. Ketamine is also a ligand of the μ-, κ-, and δ-opioid receptors (MOR partial agonist, agonist of KOR and DOR), a sigma σ1 and σ2 receptor agonist, a (presumably agonistic) ligand of the serotonin 5-HT_{2A} receptor, a weak (presumably antagonistic) potentiator of the serotonin 5-HT_3 receptor, as well as a competitive muscarinic acetylcholine receptor antagonist, acting mainly on M_1, the most common muscarinic subtype in the cortex and hippocampus. It also acts as a negative allosteric modulator of nicotinic acetylcholine receptors (mainly α7, α4β2), as well as an indirect agonist of the AMPA receptor. It is also a weak inhibitor of nitric oxide synthase and a cholinesterase inhibitor. Its inhibitory effects on the reuptake of serotonin, norepinephrine and dopamine, although measured, are dose-dependent, with SERT inhibition being the weakest of the three. Ketamine's partial agonism the high-affinity state of the dopamine D2 receptor is still considered controversial and open to interpretation and further research (Can et al. 2016). Ketamine's complex pharmacodynamics becomes evident in situations of overdose when even receptors with weak affinity may be activated. Ketamine's main antidepressant mode of action was long thought to be through the modulation of glutamate transmission (Zhang & Hashimoto 2019). Via antagonism of the NMDA receptor on GABA-ergic inhibitory interneurons, it was thought to stimulate glutamate release

by pyramidal cells in the prefrontal cortex, which should lead to increased synaptogenesis in this part of the brain (Abdallah et al. 2014). Glutamate transmission basis of ketamine's antidepressant action has recently been criticized, given that preclinical studies indicated that (2R,6R)-hydroxynorketamine, a metabolite of arketamine with negligible affinity for the NMDA receptor, may be more a effective antidepressant than esketamine (Garay et al. 2018, Hashimoto 2019). For these reasons, in 2019, arketamine and (2R,6R)-hydroxynorketamine both entered clinical trials for the treatment of depression. The antidepressant effect of ketamine is thought to be achieved by activation of the connections between the anterior cingulate cortex and amygdala and acute inhibition of the lateral habenula which can be considered "anti-reward center" in the limbic system, projecting to and inhibiting the mesolimbic reward pathway and modulating other limbic areas (Chen et al. 2018). Furthermore, ketamine affects neuroplasticity in an indirect way, through the enhancement of brain-derived neurotrophic factor (BDNF) production, via the inhibition of glycogen synthase kinase 3 and through the stimulation of mammalian target of rapamycin (mTOR) signaling in the prefrontal cortex (Roy et al. 2020).

Esketamine has approximately 3 to 4 times stronger affinity for NMDA receptors, compared to racemic ketamine. Unlike racemic formulation, it has not been found to interact with sigma receptors. While, as of yet, no antidepressant superiority of intravenous esketamine over arketamine or racemic ketamine has been found, intranasal esketamine seems less potent than racemic intravenous infusion, because of 50% lower bioavailability of the intranasal formulation. Nevertheless, esketamine was found to offer better neurocognitive protection, including, but not limited to faster rehabilitation of neuronal functioning (through atrophy reversal and neurogenesis promotion) as well as fewer episodes of anterograde amnesia, compared to other formulations of ketamine. This may be due to esketamine's superior mTOR signaling in the prefrontal cortex, which has not been detected in arketamine studies, so far. On the other hand, arketamine was found to possess less dissociative side effects and is therefore less prone to diversion and possible abuse. Arketamine could, thus, be a safer alternative to both esketamine and racemic ketamine.

NOVEL ANTIDEPRESSANT

Depression is one of the most frequent mental disorders, with prevalence up to 20-25% in general population. While psychotherapy and social therapy play a great role in depression rehabilitation, antidepressant psychopharmacotherapy remains the golden standard in the initial treatment of depressive episodes, even though in one third of cases, patients will fail to respond to the antidepressant therapy. Whereas most current antidepressants produce some benefits within the first ten days of use, full improvement might not be seen for two or three months. Rapid-acting antidepressant therapeutics may be limited to older drugs with a significant side effect burden (clomipramine), novel drugs (agomelatine) or non-antidepressant drugs (low-dose sulpiride, low-dose amisulpride). The local availability of these medications can be a limiting factor in treatment, more often than not. Ketamine and esketamine have been used as anesthetics for several decades all around the world, with known pharmacokinetics and side effect profiles. In 2000, it was found that administration of a subanesthetic dose of ketamine lead to the rapid remission of an acute depression case. The first placebo-controlled study by Berman and colleagues found noticeable results in reduction of depressive symptoms, as measured by Hamilton Depression Rating Scale (HAM-D) and self-rated Beck Depression Inventory, after a single intravenous infusion of a racemic mixture of ketamine (given as 0.5 mg/kg). Since then, numerous studies have proven fast-acting antidepressant effects of intravenous and intranasal ketamine in patients with depression. In the majority of patients, its antidepressant effects may linger up to seven days. Repeated applications of ketamine have been proposed in first-treatment non-responders since no tachyphylactic effects to antidepressant properties of ketamine has ever been detected (Rakesh et al. 2017). Ketamine has antidepressant, antisuicidal and antianhedonic actions, all of which may be independent one from another.

Intravenous or intranasal ketamine has been used as a rapid-acting antidepressant as well as a therapy of choice in treatment-refractory depression, in which it can rival (or be used synergistically with) electroconvulsive therapy. Along with lithium salts and clozapine, it is one of the few psychotropic drugs with proven antisuicidal effects, but with an additional advantage of rapid onset of action, with effects observed within minutes. Positron emission tomography imaging findings have shown that reductions in suicidal ideation after intravenous ketamine infusion correlate with decreased regional cerebral glucose metabolism in the infralimbic cortex (Brodmann area 25). BDNF may be involved in enhanced antisuicidal response to ketamine (Levinstein & Samuels 2014). Ketamine's antidepressants effects are beneficial in both unipolar and in bipolar depression, that is, there is no associated risk of manic switch. Low subanesthetic doses of ketamine have also been tried in the treatment of substance use disorders, including alcoholism, with some success (Azhari et al. 2020).

RISKS

Even antidepressant, subanesthetic doses of ketamine, have some abuse potential, due to its psychomimetic, primarily dopaminergic effects (Strong & Kabbaj 2018). Increased dopamine levels in frontal

cortex after ketamine application may be responsible for antidepressant as well as dissociative effects, as reflected by significant correlations between Clinician-Administered Dissociative States Scale (CADSS) and HAM-D scores reported up to seven days after an intravenous application of ketamine (Niciu et al. 2018). Dopamine release in the nucleus accumbens may be linked with reinforcement, which can become problematic, considering short duration of ketamine's psychomimetic and euphoric effects.

Optimal dosing can also be an issue. Usually given on a mg/kg basis, it can present an obstacle in patients with a higher BMI because they can be exposed to a larger cumulative dose of ketamine and thus experience more severe side effects. Routes of administration can also influence the results, intravenous and intramuscular being more reliable than others. The problem of possible toxicity with long-term administration has likewise not been thoroughly accessed.

Given the fact $GABA_A$-ergics (benzodiazepines, Z-drugs, alcohol) can hinder antidepressant effects of ketamine (Frye et al. 2015), it is recommended that patients cease taking them at least 12 hours (preferable 24 hours) before ketamine administration. Ongoing addiction to $GABA_A$-ergics could be considered a contraindication to ketamine treatment. Other contraindications include cardiovascular diseases, such as unstable angina, history of a recent myocardial infarction, cerebrovascular disease, acute porphyria, pheochromocytoma, penetrating eye trauma or high intraocular pressure. Ketamine is, obviously, not recommended for people with psychotic disorders.

The most frequent side effects in patients receiving ketamine are dizziness, blurred vision, headache and nausea, but they seem to fade away within 90 minutes after the discontinuance of ketamine therapy. In ketamine-abusing population, tachycardia, vomiting and altered body perception are more common, which can be explained by the fact that the larger doses are normally used. The most dramatic psychomimetic effect of ketamine is a k-hole state, described by its users as a trance-like, near-death, out-of-body experience (Curran & Monaghan 2001). Chronic use of high doses of ketamine (5 g/day or more) can give way to ketamine-induced ulcerative cystitis ("K-bladder") and other urinary problems which are self-limiting upon discontinuation of ketamine use (Middela & Pearce 2011).

Ketamine was considered, for many years, a cognition-impairing drug. It used to be studied as the example of a schizophrenia model, based on the NMDA-receptor hypofunction hypothesis (Frolich & Van Horn 2014), mimicking positive, negative and cognitive symptoms of schizophrenia. In 1989, psychiatry professor John Olney reported that ketamine caused irreversible changes, known as Olney's lesions, in two small areas of the rat brain. Similar changes have not been described in humans (Schwartzman et al. 2011). It was found that ketamine produced a dose-dependent impairment of episodic and working memory, independent of concomitant dissociative symptoms (Morgan et al. 2004). Spatial memory deficits in heavy ketamine users, as well as medial temporal lobe changes were also noticed (Morgan et al. 2014). On the other hand, lower, subanesthetic doses of ketamine have been shown to have neuroprotective action, independent of its antidepressant effect (Permoda-Osipet et al. 2015). There seems to be a dose- and a time-dependent curve between ketamine positive and negative effects on cognition. Infrequent recreational ketamine use (averaging 3.25 days of use, or less, per month) appears not to be associated with apparent cognitive impairment (Morgan et al. 2010).

BETWEEN USE AND ABUSE

In 2019, the U.S. Food and Drug Administration (FDA) approved esketamine in the form of a nasal spray, to be used with an oral antidepressant, for adults with treatment-resistant depression or depressive disorder with suicidal thoughts or actions. Due to the risk of side effects such as sedation or dissociation, the drug is only available through a strictly regulated distribution system, popularly known as "ketamine clinics" (Park et al. 2019). The high cost of the spray currently limits its widespread use. Still, this has not stopped it from being diverted to illicit market, in the form of a highly sought-after "k-spray" (Sassano-Higgins et al. 2016). Because ketamine is a drug with abuse potential, it might not be recommended for treatment-resistant depression in people with a history of co-morbid substance use disorder. Furthermore, it remains to be investigated whether people with personality disorders would be more prone to ketamine misuse, as it is frequently the case with other psychoactive drugs of abuse (Liu et al. 2016). Ketamine abuse may be underreported since it is not routinely tested through blood or urine toxicology screening (Sassano-Higgins et al. 2016).

Ketamine should not be taken together with alcohol, benzodiazepines, sodium oxybate, or γ-butyrolactone, because of the increased risk of ataxia and sedation. There is no single antidote for ketamine overdose. Supportive therapy is used. Opioid antagonists like naltrexone, which were found to have antidissociative effects in treatment of derealization and depersonalization symptoms, were found to attenuate antidepressant and antisuicidal effects of ketamine. This could convey an impression of ketamine's antisuicidal and antidepressant mechanism being intertwined with its dissociative effects. Still, more studies are needed to prove (es)ketamine therapeutic efficacy, in direct comparison with standard therapeutic options for conditions esketamine is indicated for, such as lithium, clozapine or electroconvulsive therapy.

CONCLUSION

Many psychoactive drugs are prone to abuse and diversion. When psychoactive drug rescheduling or legalization is done, it should be so to benefit users and/or to prevent them from possible harm caused by exposure to a psychotropic drug. There is such a loose line between "soft" and "hard" drugs. Drugs like ketamine can exert devastating effects on their users, including psychotic states and unpredictable behavior. Therefore, preventive strategies must be developed in order to reduce harm in susceptible individuals while providing optimized therapeutic effects in controlled, expert-guided situations, to those who may benefit from their treatment. The line between a psychoactive drug of abuse and a licensed medication can be blurry, and the trends and patterns of therapeutic use and illicit abuse are prone to cultural, social and political factors. Strict guidelines on ketamine medical use in psychiatry must be developed in order to prevent its potential overprescribing and consequent misuse, abuse or diversion.

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Conflict of interest:

All authors report no biomedical financial interest or potential conflicts of interest.
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Contribution of individual authors:

All authors contributed to writing of this paper equally.

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