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Ketamine in affective disorders – expectations and limitations

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Abstract

Classified as dissociative psychedelic, ketamine is a psychoactive agent whose exact mechanism of action has not been fully elucidated. In human and veterinary medicine ketamine is administered during preoperative analgesia. In anesthesiology it is employed either during induction of complex anesthesia or rarely, as a mono-anesthetic agent implemented in short-time procedures that do not cause visceral pain. Hallucinations, nausea, vomiting and elevation of systemic and intracranial pressure may be listed among adverse drug reactions limiting the use of ketamine. Ketamine is believed to exert antidepressant effects by antagonizing N-Methyl-D-aspartate receptor (NMDAR), combined with its presumptive inhibitory action on noradrenaline and serotonin transporter. Unlike other antidepressants, requiring weeks to exert apparent effects, ketamine relieves depressive symptoms within hours from administration. First reports on ketamine efficacy in the treatment of depressive episode come from 2000. The use of ketamine appears to be beneficial in patients who

have exhausted other possible pharmacotherapeutic options. Current data suggest that single ketamine infusion is suitable for patients with treatment-resistant unipolar or bipolar depression without psychotic features, and with no previous history of psychoactive substance abuse. The prospective therapeutical applications of ketamine in the treatment of affective disorders are promising, however, further comprehensive research is still required.

Keywords: ketamine, NMDA antagonist, affective disorder, depression

INTRODUCTION

Ketamine is a multifunctional organic chemical compound with the molecular formula $C_{13}H_{16}ClNO$, and a psychoactive agent classified as dissociative psychedelic. In human and veterinary medicine ketamine is administered during preoperative analgesia. Its pharmacological effects resemble those of dextromethorphan (DXM) and phencyclidine (PCP), however, are of significantly shorter duration and without certain adverse drug reactions (PubChem)(DrugBank). Ketamine has analgesic properties as well. In anesthesiology it is employed either during induction of complex anesthesia or rarely, as a mono-anesthetic agent. As a mono-anesthetic it is suitable for short-time procedures, which do not evoke visceral pain. Ketamine is used during plastic surgeries and painful burn dressing changes, in selected neurologic and radiologic procedures, in children requiring immobilization or in cases of difficult assessment of airway patency (https://bazalekow.mp.pl/leki/doctor_subst.html?id=442). It as well applied in multiple anesthetic procedures in a single patient (e.g. complex anesthesia in combination with other pharmaceuticals - benzodiazepines, barbiturates, neuroleptics) (DrugBank)(kartacharakterystykiproduktu Sigma-Aldrich).
A specific type of narcosis, called dissociative anesthesia, is elicited by ketamine. During dissociative anesthesia certain central nervous system (CNS) structures are undergoing selective inhibition (loss of consciousness), while the others are simultaneously stimulated (catalepsy, eyeball movement, hallucinations). The anesthetic dose of ketamine equals 1-2 mg/kg bw (PubChem)(DrugBank)(kartacharakterystykiproduktu Sigma-Aldrich)(Rybakowski 2013). Analysis of EEG records indicate functional dissociation between limbic system and neocortex, that occur during ketamine narcosis (https://bazalekow.mp.pl/leki/doctor_subst.html?id=442). Ketamine is found under several brand names: Narkamon, Ketanest and Kalypsol (DrugBank).
In 1960s analgesic and pain relieving properties of ketamine, derived from phencyclidine and cyclohexylamine, had been discovered. The occurrence of presumptive dissociative effects or hallucinations had been noted as well. In addition, ketamine finds application in chronic therapy of post-surgical cancer patients and neuropathic pain (Kotlińska-Lemieszek et al.,

2003). Recently, ketamine demonstrated curative potential in major depressive disorder (MDD) and depression in bipolar affective disorder (Grady et al., 2017) (Li et al., 2011).

MECHANISMS OF ACTION

Ketamine exerts consecutive effects following intravenous (IV) administration:

- facial analgesia after 20 seconds post-injection;
- subsequent loss of contact with a patient and presence of characteristic vertical and horizontal nystagmus, involuntary movements or vocalization may be present;
- return of consciousness after 15 minutes post-injection (PubChem)(kartacharakterystykiproduktu Sigma-Aldrich).

Non-competitive inhibition of glutamatergic N-Methyl-D-aspartate receptor (NMDAR) by ketamine had been linked with pain relieving, dissociative and neuroprotective properties (Grady et al., 2017) (Skolnick et al., 2009). In high serum concentrations, ketamine may also interact with opioid receptors enhancing analgesic effects. Ketamine is believed to exert antidepressant effects by antagonizing N-Methyl-D-aspartate receptor, combined with its presumptive inhibitory action on noradrenaline and serotonin transporter (Grady et al., 2017) (Skolnick et al., 2009) (Zhao, Sun, 2008) (Tuck et Ghazali, 2017).

Given all of the above, administration of ketamine results in analgesia, tachycardia, increase in systemic blood pressure, memory and cognitive function distortions and dose-dependent visual alterations (Grady et al., 2017). Ketamine demonstrates poor bioaccessibility when given orally (17 to 20%); therefore, intravenous injections remain the principle route of administration. CYP3A4, 2B6 and 2C9 are the hepatic enzymes responsible for ketamine biotransformation (Hijazi, Boulieu, 2002).

Since first intravenous administration of ketamine in the treatment of depression and bipolar disorder, it may pose certain challenges. Some authors claim that prospective therapeutical applications among these type of patients are relatively promising (Grady et al., 2017).

ADVERSE DRUG REACTIONS

Hallucinations, nausea, vomiting and elevation of systemic and intracranial pressure may be listed among adverse drug reactions limiting the use of ketamine. Therefore, it is administered in combination with benzodiazepines (diazepam, midazolam) and barbiturates (thiopental) to attenuate the above-mentioned. In addition, the drug may precipitate depression or provoke excessive stimulation of the respiratory centre. Long-lasting treatment with ketamine results in urinary tract distortions (DrugBank)(kartacharakterystykiproduktu Sigma-Aldrich).

NON-MEDICAL APPLICATIONS

Alike PCP and DXM, ketamine is a dissociative psychedelic. Strong psychoactive effects exerted by this agent rationalize the recreational

drug-use. The consciousness-altering properties of ketamine comprise: depersonalization, derealization, dissociation from the body, perturbed perception of the flow of time, colorful visions and visual effects resembling dreams and at high doses loss of connection with reality. The subjective state experienced after sufficiently high doses of ketamine is commonly known as the „K-hole”. Apart from MDMA and GHB, ketamine is the most popular club drug in western countries (DrugBank) (Smith et al., 1981). From 2005 onward, in Poland, ketamine is listed in group II-P of the Act on prevention of drug abuse, however, it does not undergo surveillance within the scope of United Nations Convention on Psychotropic Substances of 1971 (DrugBank)(kartacharakterystykiproduktu Sigma-Aldrich).

DEPRESSION TREATMENT

KETAMINE AND PLACEBO

The main focus of a randomized, double-blind study by Zarate et al. was to verify the possibility of achieving rapid antidepressive response with use of ketamine in 18 patients resistant to treatment of unipolar depression. The inclusion criteria were as follows: males and females aged 18 to 65, hospitalized for recurrent MDD without psychotic features, who did not respond to at least two previous attempts of antidepressive treatment (Zarate et al., 2006). Patients had to score 18 or higher on the Hamilton Depression Rating Scale during screening examination. Before receiving the first dose of ketamine or placebo, subjects had to have negative history of psychoactive substance abuse for 3 months at least, negative urine toxicology testing and had not been administered any treatment for 2 weeks, prior to study entry.
The primary end point was the change in the Hamilton Depression Rating Scale scores from 60 minutes before infusion to 40, 80, 110 and 230 minutes after infusion. Scales were also applied 1, 2, 3 and 7 days after infusion. Participants received ketamine 0.5 mg/kg intravenously infused over 40 minutes, or 0.9% salt on 2 study days, 1 week apart. Ketamine showed statistically significant improvement over placebo, starting at 110 minutes after infusion and lasting until day 7 ($p < 0.05$). Adverse drug reactions including: distorted perception, confusion, increased systemic blood pressure, euphoria, vertigo and elevated libido were more prevalent in the ketamine group. None of the above were clinically significant and subsided within 80 minutes from infusion (Rybakowski 2013) (Zarate et al., 2006).
A randomized, double-blind study by Diazgranados et al. was aimed at establishing whether ketamine evokes rapid antidepressive response in 18 patients resistant to treatment of depression in bipolar affective disorder. Inclusion criteria were: males and females aged 18 to 65, hospitalized for depression episode in type I or II bipolar disorder without psychotic features, after treatment failure with a previously set antidepressive treatment protocol and unsuccessful prospective treatment attempt with

lithium or valproate during hospitalization. Qualified patients were experiencing episode of MDD for at least 4 weeks at the time, and scored at least 20 in Montgomery-Asberg Depression Rating Scale (MADRS) during screening. Before first administration of ketamine or placebo, patients were negative for psychoactive substance abuse during at least 3-month period, had no significant suicide risk assessed clinically, were not administered with psychotropic medications other than lithium (serum concentration levels 0.6-1.2 mEq/L) and valproate (50-125 ng/ml) for at least 2-week period prior to randomization (5 weeks for fluoxetine). The exclusion criteria were as follows: serious and unstable condition, pregnancy and lactation, previous treatment with ketamine (Diazgranados et al., 2010).

The primary end point were changes in MADRS scores from 60 minutes before infusion to 40, 80, 110 and 230 minutes post infusion. Rating scales were also applied at 1,2,3,7,10 and 14 days after ketamine administration. Patients were given ketamine 0.5 mg/kg bw over a 40-minute intravenous infusion or 0.9% saline solution on 2 study days, 2 weeks apart. Ketamine demonstrated depressive symptoms improvement versus placebo starting at 40 minutes and lasting through day 3 ($P < 0.001$). Comparisons made at days 7, 10 and 14 were not statistically significant ($P=0.21$, $P=0.13$ and $P=0.09$, respectively).

Adverse drug reactions that were more common within ketamine study group comprised: dissociation, mouth dryness, tachycardia and elevated blood pressure. None of the above were significantly intense and all retreated during 80 minutes post-infusion (Diazgranados et al., 2010).

Experiment conducted by Lapidus et al. was the first randomized investigation concerning clinical effects after rostral application of ketamine. Verification of the rapid antidepressive effect occurrence after single rostral administration of 50mg of ketamine in patients with severe depression was within the scope of this study. Inclusion criteria were as follows: males and females aged 21 to 65 primarily diagnosed with MDD without psychotic features, with at least one previous therapeutic failure. Patients were subjected to thorough clinical assessment - they had to score 30 and above in a scale rating depressive symptoms, and present with negative results of urine toxicology testing. Female patients in fertile age had to take adequate contraceptive measures at the time of the study. All the study subjects could have been administered with fixed, balanced doses of antidepressants or other psychotropic medications. Exclusion criteria consisted of: unstable clinical condition, high suicidal risk, using psychotropic substances during 6 months prior to investigation, any psychotic, bipolar or developmental disorders, disorders following ketamine or PCP intake and pregnancy (Lapidus et al., 2014).

The primary end point was a change in MADRS score 24 hours after infusion of ketamine or placebo. Rating scales were also applied 60 minutes before the procedure and 40, 120 and 240 minutes after infusion. Scores were measured 1,2,3 and 7 days after drug administration as well. Eighteen subjects received 50mg ketamine or 0.9% saline intranasally through an LMA MADgic mucosal atomization device on 2 study days, 1 week apart. Compared to placebo, depressive symptoms were significantly reduced ($t = 4.39$; $p < 0.001$) in ketamine group 24 hours after

intervention. A mean change in MADRS score between ketamine and placebo groups equaled 7,6 ± 3,7 (95% confidence interval [CI] = 3.9–11.3).
Memory deterioration and fatigue were the adverse drug reactions predominating in ketamine recipients group. None of the above adverse drug reactions were severe, and both retreated within 4 hours from medical intervention (Lapidus et al., 2014).

KETAMINE AND MIDAZOLAM

Study by Murrough et al. was aimed at determining antidepressive potential of ketamine in the treatment-resistant MDD. The inclusion criteria comprised: age 21 to 80, primary diagnosis of MDD, at least two treatment failures with antidepressants, history of at least one MDD episode or chronic MDD with >32 test score at initial assessment and 24 hours prior to infusion. Patients were restricted from taking any antidepressant or psychotropic medications during 1 to 4 weeks preceding infusion. Subjects with history of psychotic or bipolar disorder, alcohol or substance abuse over preceding 2 years, unstable medical condition, serious suicidal intents, score <27 in Mini Mental State Examination (MMSE) or receiving prohibited medications were excluded from the study. 73 persons were randomly assigned to groups treated with either ketamine or midazolam. 48 patients received ketamine 0.5 mg/kg bw and the remaining 25 patients were given midazolam 0.045 mg/kg bw both infused over 40-minute IV infusion. Decrease in depression severity assessed with MADRS 24 hours post-infusion constituted the major end point. A sample size of 72 randomized subjects in 2:1 ratio (ketamine vs midazolam) would provide 80% power to detect change in MADRS score at 24 hours post-infusion as a function of treatment. 47 investigated patients from the ketamine group and 25 from the midazolam arm were included in a modified intention-to-treat analysis. Baseline characteristics were similar for the two groups. At 24 hours, mean MADRS scores for ketamine and midazolam groups were 14.77 (95% CI = 11.3–17.80) and 22.72 (95% CI = 18.85–26.59) respectively, constituting a statistically significant difference between the groups ($p<0.001$, degrees of freedom [df]=68). When adjusted to baseline values and site, a statistically significant difference existed between the two groups (95% CI = 3.20–12.7) with no difference between sites ($P = 0.43$, df = 1.70). Subject's scores were analyzed after 1,2,3 and 7 days after infusion to assess durability of ketamine's effects. Evaluation indicated no changes over time as a function of treatment ($F = 5.93$, df = 1.202, $p < 0.58$), but revealed main effects for time ($F = 7.62$, df = 1.202, $P < 0.006$) and treatment ($F = 5.93$, df = 1.202, $P < 0.02$). The study showed that over time subjects from ketamine group had lower MADRS scores (mean 16.93; 95% CI = 14.03–19.82) than in midazolam group (mean 23.19; 95% CI = 19.02–27.34; $t = 2.33$, df=202, $p < 0.02$).
Beneficial effects of ketamine had disappeared starting from 3 days after infusion. On day 7, positive results on depression, depicted by MADRS scale, did not show significant differences between the groups. Adverse events lasting up to 4 hours, and being more frequent in ketamine group were dizziness, headaches, blurred vision, nausea and vomiting,

xerostomia, insufficient coordination, poor concentration and anxiety. Among patients administered with ketamine, 17% reported significant dissociative symptoms that subsided within 2 hours after infusion.

Murrough et al. dedicated another experiment to the assessment of cognitive functioning after single dose of ketamine. Reduction of MADRS score by 50% comparing to the initial values was the primary end point. 62 patients were double-blind randomized to receive single intravenous infusion of 0.5 mg/kg ketamine (n=43) or 0.045 mg/kg of midazolam (n = 19) over 40-minute period. Several different neurocognitive evaluations were conducted at the beginning of the study, including processing speed (category fluency, Trails A, Brief Assessment of Cognition in Schizophrenia Digit Symbol), working memory (Wechsler Memory Scale-III Spatial Span, letter-number), verbal (Hopkins Verbal Learning Test learning and delay) and visual learning (Brief Visual Memory Test learning), and reasoning/problem solving (Neuropsychological Assessment Batter Mazes). The impact of time, treatment conditions and response to antidepressant medications were analyzed with variance analysis and logistic regression models. Changes in data processing speed ($F = 6.58$; $p = 0.013$), verbal ($F = 6.80$; $p = 0.012$) and visual learning ($F = 6.48$; $p = 0.014$) proved to be significantly better in the midazolam study arm. No differences in working memory or reasoning were observed. It was determined via linear regression that ketamine responders had significantly slow processing speed at baseline (T-score = 43.37 ± 8.78) compared to ketamine non-responders (T-score = 49.24 ± 10.1; $F = 4.36$; $P = 0.043$).

Morrough et al. proposed a well-designed study with a sample size sufficiently large for the subject, strict inclusion and exclusion criteria. Authors applied appropriate statistical analyses (Murrough et al., 2013) (Murrough et al., 2015).

In recent years, trials had been made to achieve permanent improvement by means of repeated ketamine infusions. Both clinical and biochemical factors contributing to the single-dose efficacy of ketamine are investigated concurrently. American researchers indicated superior effects of treatment with ketamine in the depression related to affective bipolar disorder especially in patients with familial history of alcohol abuse. Such relationship has been proved in our study group as well. Among biological factors related to single-dose effect of ketamine in depression in course of bipolar disorder, a connection has been observed for brain-derived neurotrophic factor (BDNF) serum fluctuations (Rybakowski, 2013d) and initial serum concentrations of vitamin B12. Furthermore, attempts have been made to employ medications with profile similar to that of ketamine. Traxoprodil is an NMDAR antagonist, selective for the NR2B subunit. It demonstrates neuroprotective, analgesic and anti-Parkinsonian properties in animal models (Poleszak et al., 2016). Research on the use of traxoprodil in depression treatment demonstrated its analogous effects to ketamine. Patients diagnosed with depression, presenting poor treatment outcome with selective serotonin reuptake inhibitors, reported rapid improvements in psychological condition after the infusion of traxoprodil. In 1/3 of patients symptoms of remission had been observed 5 days after infusion. No other reports concerning replication of the aforementioned results have been published so far (Rybakowski 2013) (Preskorn et al.,

2008). The use of similar medication, metodoxine, has been proposed by Italian authors. Apart from inhibiting NMDAR, the pharmaceutical influences reuptake of neurotransmitters and modulates both opioid and sigma receptors (Rybakowski 2013) (Coppola and Mondola, 2013).

CONCLUSIONS

Ketamine precipitates immediate symptoms alleviation in patients resistant do treatment of depression and bipolar disorder. Several minor clinical studies have indicated, that a rapid antidepressant response is achieved within 2 to 4 hours after administration of a single 0.5 mg/kg bw dose of ketamine over a 40-minute IV infusion. The maximal antidepressant effects emerge at 24 hours post infusion, and persist up to 7 days. A meta analysis byRomeo et al. (Romeo et al., 2015) presents the efficacy of ketamine versus placebo at 1, 2, 3–4, 7 and 14 days of treatment of drug-resistant depression. The advantage of ketamine antidepressant potential over placebo proved to be statistically significant from day 1 to 7. Repeated analyses were made to verify possible changes of efficacy in unipolar and bipolar disorders. Ketamine did not evoke significant improvement from day 1 to 7 in patients with unipolar disorder. With respect to the patients with bipolar disorder - effectiveness on day 4. Ketamine offers multiple benefits to patients suffering from treatment-resistant depression or depression related to bipolar disorder, including novel mechanism of action, rapid antidepressant effect and lack of specific, previously known adverse events of antidepressant medications (body mass deviations, sexual disturbances). Despite quick onset, the antidepressant effects exerted by ketamine seem to be temporary (lasting several days to weeks) after single administration. In addition, ketamine has a characteristic unfavorable profile with the potential of abuse. Reported adverse events comprise psychotic and dissociative effects, blood pressure and heart rate fluctuations, blurred vision. Another considerable risk is posed by current practice - the lack of prescription, distribution and ketamine monitoring regulations (Grady et al., 2017). A growing number of evidence supports previous considerations that administering NMDAR antagonist - ketamine, alleviates symptoms of depressive syndrome. This particular therapy had been implemented in a sparse number of patients until present. There exist little data concerning optimal dosage and frequency of administration as well. Although possibly temporary in nature, the effect obtained after single ketamine infusion is substantial. Therefore, such application pattern is worth considering in patients with high suicidal risk, as supported by results of the study by Diazgranadoz (Diazgranados et al., 2010) (Smith et al., 1981).
The use of ketamine appears to be beneficial in patients who have exhausted other possible pharmacotherapeutic options. Current data suggest that single ketamine infusion is suitable for patients with treatment-resistant unipolar or bipolar depression without psychotic features, and with no previous history of psychoactive substance abuse. Nonetheless, further comprehensive research is still required (Grady et al., 2017) (Tuck et Ghazali, 2017). The psychomimetic potential of sub anesthetic-dose ketamine is the key issue. Possibility of combined

treatment with ketamine and other antidepressant medications remains an open question. Is this certainly safe? The answer still requires additional studies and deeper observation. Until now, ketamine therapy has been essentially applied in patients with unipolar disorder or when establishing the predominant polarity was impossible due to imprecise diagnosis of Major Depressive Disorder. The current results of aforecited studies seem to encourage future research on the topic (Gosek et al., 2012) (Abdallah et al., 2017).

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