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Conference paper

SHORT-TERM KETAMINE ADMINISTRATION IN TREATMENT-RESISTANT DEPRESSION PATIENTS: FOCUS ON ADVERSE EFFECTS ON THE CENTRAL NERVOUS SYSTEM

Adam Włodarczyk, Wiesław Jerzy Cubała, Joanna Szarmach, Antonina Małyszko & Mariusz S. Wiglusz

Department of Psychiatry, Faculty of Medicine, Medical University of Gdansk, Gdańsk, Poland

SUMMARY

Major depressive disorder (MDD) is a recurrent, incapacitating psychiatric illness which will be the second most disabling disease worldwide by the year 2020. There is a rising promise in a N-methyl-D-aspartate (NMDA) receptor antagonist, ketamine, which may be used in the treatment of resistant depression. Many of the studies are in favor of the drug, even in single dose application, with effects appearing in minutes to hours from administration. However, there is a need to evaluate the benefits and risks regarding psychomimetic, psychiatric, neurologic, and cognitive adverse effects of ketamine administration. The most distressing symptoms which appear most frequently during ketamine administration are dissociative symptoms, which can be quantified as a CNS adverse drug reaction. Results generally show that a single infusion of ketamine is efficacious and well-tolerated, while dissociative symptoms tend to abate within 2 hours after ketamine administration. As studies show single doses of ketamine should be definitely considered as an option in TRD patients with/without suicidal thoughts, even though it could not provide remission, or the effect could be temporary, but improving patients' quality of life by reducing depressive symptomatology should be a major asset while considering this particular procedure, particularly in inpatients.

Key words: *ketamine – MDD - treatment resistant depression - central nervous system - safety*

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INTRODUCTION

Major depressive disorder (MDD) is a recurrent, incapacitating psychiatric illness which will be second most disabling disease worldwide by the year 2020 (Martínez-Cengotitabengoa & González-Pinto 2017). Almost one-third of the MDD patients do not achieve remission suffering from treatment-resistant depression (TRD) (Correia-Melo et al. 2017). It also is associated with substantial mortality (American Psychiatric Association 2000). There is a great need to develop treatments which could rapidly relieve or significantly decrease MDD symptomatology. There is a rising promise in used since early 1960s for anesthesia purposes, a N-methyl-D-aspartate (NMDA) receptor antagonist, ketamine (Haas & Harper 1992). The mechanism of action of ketamine is different from majority of prescribed antidepressants with selective serotonin reuptake inhibitors being the most frequently given by physicians (Cohen et al. 2017). The proposed mechanism of action is to affect glutamate (major excitatory neurotransmitter in mammalian brain (Włodarczyk et al. 2017), increasing brain-derived neurotrophic factor (BDNF) release, stimulating synaptogenesis. There are strong data that expression reduction of BDNF is associated with MDD (Guilloux et al. 2012, Lusher & Fuchs 2015).

The aim of this paper is to evaluate the benefits and risks regarding psychomimetic, psychiatric, neurological, cognitive adverse effects of ketamine, as we called 'Central Nervous System (CNS) adverse drug effects' of single-doses of ketamine in MDD patients.

KETAMINE USE IN DEPRESSION

Ketamine is a racemic mix of S-ketamine and R-ketamine. With drug development an enantiomer, intranasal S-ketamine, is in clinical use being approved by The Food and Drug Administration in March 2019 (Food and Drug Administration, Highlights Of Prescribing Information, 2018). The S-ketamine is more potent NMDA antagonist, more potent agonists of μ-opioid receptor and less potent sigma receptor agonist than R-ketamine (Andrade et al. 2017a), which can show its advantage over ketamine regarding more analgesic, more anesthetic, less psychomimetic and other adverse effects, therefore it is preferred acting as psychiatric drug. The majority of studies although are based on ketamine racemic mix intake due to its more common availability (Correia-Melo et al. 2017, Segmiller et al. 2013).

Since the first study by Berman et al. (2000) with ketamine administered intravenously there were several other researches exploring ketamine predominantly in TRD treatment with ketamine (Andrade et al. 2017a, Feifel et al. 2017). Many of them are in favor of the drug, even in single-use, with effects appearing in minutes to hours from administration (Correia-Melo et al. 2017, Feifel et al. 2017, Kim & Mierzwinski-Urban 2017, Möhler 2012) lasting mostly up to 7-14 days, interestingly often with antisuicidal effect (Al-Shirawi et al. 2017, Kim & Mierzwinski-Urban 2017). Chiefly, ketamine in intravenous doses is administered in 0.5 mg/kg in 40 minutes (Feifel et al. 2017), nonetheless, there is also evidence for faster infusions (Correia-Melo et al. 2017). Doses below 0.5 mg/kg of ketamine seem

Table 1. Comparison between ketamine route/dose safety

Route	Dose	Comment
Intravenous	0.5 mg/kg	no serious adverse events (SAE), most studied way of administering
Intranasal	50 mg	no SAE, adverse events disappeared after max 4h.
Sublingual		no significant studies found on single-dose administration
Subcutaneous		no significant studies found on single-dose administration
Intramuscular	0.25 mg/kg; 0.5 mg/kg	no SAE, results similar in both doses, may appear painful

Table 2. Comparative incidents of neuropsychiatric adverse effects in studies with ketamine/ esketamine in different routes of administration (Berman et al. 2000, Diazgranados et al. 2010, Shiroma et al. 2014, Singh et al. 2015, Sos et al. 2013, Loo et al. 2016, Murrough et al. 2013)

	Most common adverse effects	
Adverse events were: ▪ well tolerated ▪ ephemeral ▪ they return to baseline within 0.5-4 hours after administration ▪ no serious adverse events were reported	Psychomimetic	loss of concentration, vivid dreams, dysphoria, anxiety and disorientation, hallucinations, thought disorder
	Dissociative	altered body perception, alter time perception, depersonalization, derealization

Table 3. Safety scales

Questionnaire	Symptoms assessed	Time
CADSS	Dissociative domain	ca. 15 min
BPRS+	Psychotic domain	ca. 10 min.
MCCB	Cognitive domain	60-90 min.

to be less effective than standard 0.5 mg/kg (Andrade 2017b, Xu et al. 2016). In studies comparing one to series of administrations of ketamine, it was stated that repeated ketamine infusions provide longer time of positive response (Segmiller et al. 2013). In a study by Hu et al. (2016), single dose of intravenous ketamine with placebo comparison, there response and remission rates were significantly higher for ketamine, respectively 92% vs. 57% and 77% vs. 14%. Moreover, even widely prescribed for anxiety, sleep disturbances, anxiety or behavioral disinhibition etc., benzodiazepine (Haas & Harper 1992), were compared (midazolam) vs. ketamine in single-dose. Although nearly one-fifth of the patients experienced dissociative symptoms, the antidepressant results were in favor of ketamine (64% of ketamine-patients vs 28% midazolam-patients with response rates), measured with Montgomery-Åsberg Depression Rating Scale (MADRS), after 24 h of infusion one or the other. The results did not differ in groups after 7 days from infusion (Murrough et al. 2013). Sublingual (oral) form of ketamine in dose 10 mg, given in bipolar depression, appeared to be better tolerated and similarly efficacious on mood and cognition in comparison to intravenous ketamine (Lara et al. 2013), unfortunately as well as in subcutaneous route literature lacks significant data on single dose of ketamine. Single dose of intranasal form of ketamine also appeared to be more efficacious than placebo, while administering ketamine intramuscularly in a dose up to 0.5 mg/kg showed significant benefit in depression (Andrade 2017b) (Table 1).

NEUROPSYCHIATRIC ADVERSE EVENTS ASSOCIATED WITH NERVOUS SYSTEM DISORDERS

The last sentence brings an important concern of ketamine not only about its efficacy but also its tolerability and safety issues. The most distressing symptoms which appears most frequently during ketamine intake are dissociative symptoms (Xu et al. 2016), which can be established as a CNS adverse effect. The most used and valuable questionnaires tend to be Clinician Administered Dissociative States Scale (CADSS) and brief psychiatric rating scale (BPRS) or four-item BPRS positive symptoms subscale (BPRS+), neurocognitive functioning, using the MATRICS consensus cognitive battery (MCCB) (Kim & Mierzwinski-Urban 2017, Short et al. 2018). In a large, double-blind, multi-center study of esketamine (nasal form) taken as an add-on to oral antidepressant treatment, showed that adverse events were mild to moderate, where most common adverse events reported in the esketamine plus antidepressant group were: dysgeusia, vertigo, dissociation, somnolence, and dizziness, each reported for less than 7 per cent of patients in the antidepressant/placebo group In that same study it dissociation was measured by CADSS and it was noted that there appeared to be a reduction in the value of symptoms reported with repeated esketamine intake over time (Daly et al. 2019) (Table 2).

Although, dissociative symptoms have been observed as positive indicator for a better antidepressant effect of ketamine (Correia-Melo et al. 2017), still they might be distressing (Segmiller et al. 2013). Results generally show that a single infusion of ketamine is efficacious and well-tolerated, while dissociative symptoms tend to disappear in a maximum of 2 hours from ketamine intake (Feifel et al. 2017, Kim & Mirzewinski-Urban 2017). As to cognition significant improvements

Table 4. Management for best practice

Patient qualification	Treatment resistant depression	
Assessment	safety during ketamine intake	BPRS+, CADSS, MCCB
Observation and follow-up	safety after ketamine intake	Montgomery-Åsberg Depression Scale
Intervention	if significant adverse event appears	Small dose of benzodiazepines, e.g. lorazepam 1mg p.o.

in some domains were observed (processing speed, verbal learning, and visual learning) of neurocognitive performance but not in others (working memory and reasoning) measured between baseline and seven days after treatment with intravenous single-dose ketamine (Kim & Mirzewinski-Urban, 2017). As for anxiety which could be also a CNS group adverse effect, if per clinical evaluation it would be significant, as it appeared in one study with part stoppage of drug infusion, single dose of 1 mg lorazepam would stop excessive anxiety symptoms (Feifel et al. 2017). Mostly, the adverse effects of ketamine tend to be mild to moderate, short-term, but when some patients experience a severe intensity of adverse effects they are not regarding CNS adverse effects group (Short et al. 2018, Xu et al. 2016).

In a several studies with ketamine hydrochloride from single up to twelve infusions per study, where groups were various in terms of patient number were compatible with each other in terms of CNS adverse effects (summarized in table 2) (Berman et al. 2000, Diazgranados et al. 2010, Shiroma et al. 2014, Singh et al. 2015, Singh et al. 2016, Sos et al. 2013, Loo et al. 2016, Murrough et al. 2013). For example, in a study with 15 patients suffering from major depression disorder carried by Loo et al. (2016), a relationship between dose and patients' response was observed between dissociative psychomimetic effects and ketamine treatment regarding all routes, but higher peak scores in the intravenous group. Analysis of CADSS scores showed no noteworthy effect for route at 40 minutes or 240 minutes after injection. CNS effects reported included mild depersonalization, derealization, altered body perception and altered time perception. Peak effects occurred up to 15 minutes after injection, resolving without intervention by 40 minutes after injection for every participant, every dose and every route of administration. Items rated from the BPRS and Item 1 of the Young Mania Rating Scale (Elevated Mood) revealed no evidence of treatment emergent mania at any time point, across routes of administration and doses. No clinically significant change in BPRS or CADSS was observed in the midazolam condition, across all routes of administration (Loo et al. 2016). In other study on a larger group (66 depressive patients) by Singh et al. (2016), during the double-blind and open-label phases, dissociative symptoms (measured by CADSS) were observed shortly (up to 40 minutes) after start of the infusion and resolved by 3 hours post-infusion maximum. The acuteness of dissociative symptoms reduced with repeated dosing. No delusions or hallucinations were observed during the study. BPRS scores returned to primary values at the 3-hour after infusion assessment in the two ketamine frequency groups in both the double-blind and open-label phases. Other evidence is showing similar results saying the BPRS score returned to a basal by less than an hour (Diazgranados et al. 2010, Sos et al. 2013), 120 minutes after infusion ends (Berman et al. 2000, Shiroma et al. 2014) or in one study in 240 minutes (Shiroma et al. 2014). In the last-mentioned study also indicates that ketamine most common adverse event were those related to Central Nervous System 'each infusion included feeling strange or unreal (58.3%), abnormal sensations (54.2%) (Murrough et al. 2013) (Table 3).

However, with scarce data on ketamine use in TRD and recent approval of esketamine nasal spray for patients with TRD who experienced remission or response after esketamine treatment, the evidence for the long-term continuation treatment applies to esketamine nasal spray in addition to oral antidepressant treatment and is known to be both clinically effective in short-term intervention as well as in the long-term maintenance treatment for preventing relapse (Daly et al. 2019).

As studies show single doses of ketamine should be definitely considered as an option with strong evidence for its safety in TRD patients with/without suicidal thoughts (Table 4).

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Adam Włodarczyk: study conception and design, acquisition of data, analysis and interpretation of data, drafting of manuscript.

Wiesław Jerzy Cubała: drafting of manuscript, critical revision.

Joanna Szarmach: analysis and interpretation of data.

Antonina Małyszko: acquisition of data.

Mariusz S. Wiglusz: critical revision.

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Correspondence:
Adam Wlodarczyk, MD
Department of Psychiatry, Faculty of Medicine, Medical University of Gdańsk
Dębinki St. 7 build. 25, 80-952 Gdańsk, Poland
E-mail: aswlodarczyk@gmail.com