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SHORT-TERM KETAMINE ADMINISTRATION IN TREATMENT-RESISTANT DEPRESSION: FOCUS ON CARDIOVASCULAR SAFETY

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SUMMARY

Ketamine is an anaesthetic and analgesic agent that demonstrates the antidepressive effect in major depression. Several administrations routes, dosing schemas and esketamine are investigated in basic and clinical research with particular focus on treatment-resistant depression (TRD) where drug demonstrates its efficacy where very limited alternatives are available. The majority of ketamine studies in TRD treatment reported no serious adverse events regardless the administration route or regimen. However, the most commonly observed adverse events following ketamine administration in antidepressive doses include general, psychotomimetic, dissociative and hemodynamic ones. The side effects are mild or moderate, well-tolerated and transient.

This paper discusses the risks regarding cardiovascular safety in MDD patients in short-term ketamine administration with particular focus on the effect on blood pressure and adverse drug reactions mitigation measures.

The increase in systolic (SBP) and diastolic (DBP) blood pressure is dose-dependent and begins shortly after administration peaking at around 30 to 50 minutes with SBP and DBP rise from 10% to 50% above predose values and resolving at approximately 2 to 4 hours after the dose administration. These changes generally are primarily asymptomatic. The elevations in SBP and DBP are observed on each dosing day with multiple administration schema.

The treatment with ketamine and esketamine is contradicted in subjects at risk of an increase in blood pressure or intracranial pressure. The current evidence indicates the blood pressure should be assessed prior to dosing with ketamine and hypertensive individuals shall receive effective lifestyle/pharmacologic management prior to treatment. Blood pressure should be monitored after dose administration until blood pressure returns to acceptable levels. If blood pressure remains elevated acute blood pressure management shall be delivered. In patients experiencing symptoms of hypertensive crisis immediate emergency care must be provided.

The unmet need for improved pharmacotherapies for TRD means the use of ketamine and esketamine is warranted therapeutic option in patients who fail to achieve a sustained remission of depressive symptoms with drugs with monoamine-based mechanisms of action. Adequate safety measures must be applied when using ketamine/esketamine in TRD subjects with particular focus on somatic comorbidities as the transient drug effect on cardiovascular system is demonstrated and of clinical significance.

Key words: *ketamine - MDD - treatment resistant depression - cardiovascular system - safety - adverse drug reactions - blood pressure*

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INTRODUCTION

Ketamine is an anaesthetic and analgesic agent that received particular interest in 2000 when Berman et al. published the results of their clinical trial demonstrating the antidepressive effect of the drug in major depression (Berman et al. 2000, McGirr et al. 2015, Rosenblat et al. 2019). With a global burden of mood disorders on humans and the limitations of the monoaminergic antidepressants available ketamine research and use flourish with recent FDA approval for intranasal esketamine in TRD (treatment-resistant-depression) use.

Ketamine is a racemate of its R- and S-enantiomers exhibiting different pharmacodynamics with majority of basic and clinical research pointing out to esketamine showing 3- to 4-fold higher affinity to phencyclidine site of the NMDA receptor than R-ketamine, corresponding with its potency in terms of anaesthesia and analgesia (Kohrs & Durieux 1998) and more favorable tolerability profile with regard to its psychotomimetic side effects (Mathew et al. 2012, Paul et al. 2009).

The mechanisms associated with ketamine antidepressant action are unclear. Still, its mode of action is different from monoaminergic antidepressants (Chiriță et al. 2015). Subanaesthetic ketamine and esketamine doses trigger a intracellular cascade that induces synaptogenesis and dendritic spine formation (Duman et al. 2012) impacting three signalling pathways hypothetically employed in a glutamate hypothesis of major depression including the brain-derived neurothrophic factor (BDNF) pathway, the mammalian target of rapamycin (mTOR) signalling pathway and AMPA receptors (Abelaira et al. 2014).

The aim of this paper is to evaluate the risks regarding cardiovascular safety in MDD patients in short-term ketamine administration with particular focus on the effect on blood pressure and adverse drug reactions mitigation measures.

KETAMINE USE IN MAJOR DEPRESSION

The seminal proof-of-concept study with ketamine demonstrated that a single, subanaesthetic dose of intravenous drug exerts a rapid and persistent antidepressive effect in major depression (Berman et al. 2000). The subsequent basic research data and clinical trials

confirmed that ketamine is effective for patients with TRD (Coyle & Laws 201, McGirr et al. 2015, Short et al. 2018) and, in somehow isolated manner, reduces the intensity of suicidal thoughts in patients with TRD (Diazgranados et al. 2010, Price et al. 2009, Price et al. 2014, Short et al. 2018).

The mechanism of ketamine action in major depression is distinct from the monoaminergic antidepressant treatments. Ketamine affects fast excitatory glutamate transmission, increases BDNF release, and stimulates synaptogenesis. The pharmacodynamics of ketamine and esketamine is well demonstrated with its clinical antidepressive effect appearing in minutes to hours post administration in line with glutamate hypothesis of major depression.

Ketamine is administered via different routes including intravenous (IV), intramuscular (IM), intranasal (IN), inhalation (nebulization), epidural, subcutaneous, transdermal, intra-articular, sublingual and oral formulations (Le Nedelec et al. 2018).

In majority of clinical reports available in the literature on patients with major depression, ketamine is used as a racemic mixture for single, intravenous 40-minute infusion in a dose equal to 0.5 mg/kg (Berman et al. 2000, Diazgranados et al. 2010, Zarate et al. 2006, Zarate et al. 2012b, Short et al. 2018). There are also studies with multiple ketamine administrations with several IV infusions (Murrough et al. 2013b, Shiroma et al. 2014, Singh et al. 2016, Short et al. 2018) with recent studies on intranasal esketamine in acute and maintenance treatment of TRD (Daly et al. 2018, Daly et al. 2019, Fedgchin et al. 2019, Popova et al. 2019). The FDA approved nasal esketamine spray demonstrates its antidepressive effect in the acute and maintenance treatment of TRD at doses of 56 or 84 mg coadministered with an oral antidepressant (Daly et al. 2019).

KETAMINE USE IN MAJOR DEPRESSION – CARDIOVASCULAR ADVERSE DRUG REACTIONS

The majority of ketamine studies in TRD treatment reported no serious adverse events regardless the administration route or regimen. The most commonly observed adverse events following ketamine administration in antidepressive doses include general, psychotomimetic, dissociative and hemodynamic ones. The side effects are mild or moderate, well-tolerated and transient as all of them cease within 4 hours post administration (Short et al. 2018) (Table 1).

However, there is the clinically significant effect on blood pressure in normotensive individuals. The transient peak increases in systolic (SBP) and diastolic (DBP) blood pressure were reported during the infusions with ketamine and esketamine as well as being observed when alternative administration route was investigated. Animal studies suggest that the increase in blood pressure produced by ketamine is due to selective activation of central cardiac stimulating mechanisms leading to an increase in cardiac output. The blood pressure levels exceeding 180/100 mmHg or heart rates exceeding 110 beats per minute in approximately 20-30% of the patients exposed to drug are reported (Short et al. 2018).

The increase in SBP and DBP is dose-dependent and begins shortly after administration peaking at around 30 to 50 minutes with SBP and DBP rise from 10% to 50% above predose values and resolving at approximately 2 to 4 hours after the dose administration. These changes generally are primarily asymptomatic. The elevations in SBP and DBP are observed on each dosing day with multiple administration schema (Daly et al. 2018, Daly et al. 2019, Fedgchin et al. 2019, Popova et al. 2019).

The blood pressure elevation rates are higher among subjects with a history of hypertension than in those without such a history. Thus, the exposure to ketamine and esketamine treatment is associated with meaningful effects on heart rate and, in particular, on blood pressure for some patients.

SAFETY PRECAUTIONS

It is of prime importance qualifying and monitoring patients' safety when using ketamine with particular focus on cardiovascular risks. The treatment is contradicted in subjects at risk of an increase in blood pressure or intracranial pressure, in particular with known aneurysmal vascular disease and with known history of intracerebral hemorrhage (Short et al. 2018).

Table 1. Ketamine associated adverse drug reaction in the treatment of tretment-resistnt depression

Type	Symptom	Comment	Timeframe
General	headache blurred vision, dry mluth, dizziness, anxiety, nausea, vomiing, faintness, sllep diorders, cognitive decline, restlessness, euphoria, increased sex drive, constipation, dysgeusia, hypoaesthesia at site of administratiuon	transistent	returns to normal up to 4 hours post-dose
Psychomeimetic	paranoia, hallucinatiobn, dellusion, thought disorder	transistent	returns to normal up to 4 hours post-dose
Dissociative	altered body and time perception, depersonalisation, derealisamtionb	transistent	returns to normal up to 4 hours post-dose
Hemodynamic	increase HR, increase SBP and DBP	transistent	returns to normal up to 4 hours post-dose

Patients with cardiovascular and cerebrovascular conditions are to be evaluated and stabilized prior to treatment initiation with exclusion of subjects with unstable or poorly controlled hypertension, history (within 6 weeks) of cardiovascular event, including myocardial infarction (MI), ischemic stroke or transient ischemic attack, hemodynamically significant valvular heart disease or New York Heart Association Class III-IV heart failure of any etiology.

Patients with a history of an MI should be clinically stable and cardiac symptom free prior to drug administration (Table 2).

Table 2. Patients with a history of an MI

Transient blood pressure increases are observed with ketamine/esketamine on treatment days The maximum value was reached at 40 minutes after the start of administration in most cases and typically returned to the predose
Few patients experience treatment-emergent transient hypertension, defined as a systolic blood pressure of 180 mm Hg or higher and/or a diastolic blood pressure of 110 mm Hg or higher
No clinically significant change in electrocardiographic findings was observed to date

KETAMINE USE IN MAJOR DEPRESSION – CARDIOVASCULAR ADVERSE DRUG REACTIONS MITIGATION MEASURES

CVD ketamine adverse drug reaction in the treatment of tretment-resistnt depression is presented in table 3.

Table 3. CVD ketamine adverse drug reaction in the treatment of tretment-resistnt depression

Common	temporary tachycaria; increase in blood pressure and heart rate
Rare	arrythmia; bradycardia

Ketamine may cause transient increases in SBP and/or DBP lasting approximately 1 to 2 hours. The current evidence indicates the blood pressure should be assessed prior to dosing with ketamine and hypertensive individuals shall receive effective lifestyle/pharmacologic management prior to treatment. Blood pressure should be monitored after dose administration until blood pressure returns to acceptable levels. If blood pressure remains elevated acute blood pressure management shall be delivered. In patients experiencing symptoms of hypertensive crisis immediate emergency care must be provided (Table 4).

Table 4. Ketamine/eskamine adeverse drug reactions in TRD

Author	Intervention	Response
Berman et al. 2000	ketamine i.v. Infusion (single)	significantly greater scores on the BPRS scale, especially the positive symptoms. Scores returned to baseline by 120 min after infusion.
Zarate et al. 2006	ketamine i.v. Infusion (single)	elevations in blood pressure, euphoria, dizziness, and increased libid; adverse effects occurring more frequently with placebo than ketamine were gastrointestinal distress, increased thirst, headache, metallic taste, and constipation. The majority of these adverse effects ceased within 80 minutes after the infusion
Diazgranados et al. 2010a	ketamine i.v. Infusion (single)	adverse events associated only with ketamine (≥10% of subjects) included tachycardia and increased blood pressure; twoubjects who experienced increased blood pressure and tachycardia returned to normal within minutes after the infusion. No adverse event was significantly different from placebo at 80 minutes or thereafter. No significant changes occurred in electrocardiography, respiratory, or laboratory values during the study.'
Diazgranados et al. 2010b	ketamine i.v. Infusion (single)	replicable to the previous study
Zarate et al. 2012b	ketamine i.v. Infusion (single)	no significant changes occurred in electrocardiogram, respiratory, or laboratory values during the study.
Sos et al. 2013	ketamine i.v. Infusion (single)	mild increases in blood pressure, emotional blunting and euphoria; majority of these effects ceased within 30 minutes after the ketamine infusion.
Murrough et al. 2013a	ketamine i.v. Infusion (uo to 6)	mild transient changes in blood pressure were observed on the infusion day; the infusion was discontinued for two patients in the ketamine group because of hemodynamic changes; in one case, a blood pressure elevation (peak, 187/91 mm Hg) unresponsive to beta-blocker therapy resulted in infusion termination after 30 minutes. The blood pressure normalized within 10 minutes of infusion cessation. In the other case, there was transient but pronounced hypotension and bradycardia that resolved without sequelae and was followed by overnight observation in the hospital

Table 4. Continues

Author	Intervention	Response
Murrough et al. 2013b	ketamine i.v. Infusion (single)	sixteen participants (67%) did not experience any clinically significant change in vital signs during any of the ketamine infusions; eight participants (33%) experienced elevated BP and/or heart rate according to pre-defined study criteria at least once during the series of infusions; one participant experienced elevated BP during the first infusion that did not respond satisfactorily to administration of antihypertensive medication, resulting in discontinuation of the infusion and study exit (maximum BP: 180/115); BP of that participant stabilized shortly after discontinuation of the ketamine infusion.
Shiroma et al. 2014	ketamine intranasal administration (single)	none of the patients experienced arrhythmia or required respiratory support during the infusions; one normotensive 32-year old patient experienced a single episode of rise in blood pressure (180/92) that required 10 mg of IV labetalol; blood pressure rapidly returned to baseline and remained normal until discharge.
Lapidus et al. 2014	ketamine intranasal administration (up to 6)	intranasal ketamine was associated with small increases in systolic BP (mean increase of 7.6 mm Hg at 40 min compared with baseline); four participants experienced treatment emergent increases in systolic BP >130 mm Hg after ketamine, and three participants experienced systolic BP >130 mm Hg after placebo. No patients had diastolic BP >100 mm Hg. There were no clinically significant elevatio ns in BP or heart rate that required intervention, and all hemodynamic changes resolved by 4 hours after infusion. No association was found between hemodynamic changes and antidepressant response to ketamine (all $p<0.05$).
Singh et al. 2015	esketamine i.v. Infusion (twice)	no clinically significant changes in laboratory tests, electrocardiograms, or physical examinations were observed; the only clinically significant vital sign abnormalities were a case of irregular breathing and a case of transient high blood pressure (both with esketamine 0.40 mg/kg dosing), which resolved within 2 hours without intervention.
Loo et al. 2016	esketamine i.v. Infusion (single)	transient increases in heart rate, systolic and diastolic blood pressure were observed with peak incidence 5–10 min after ketamine injection in the IV group, and 10–15 min after ketamine injection in the IM and SC groups; aross groups, increases in heart rate did not exceed 120% of baseline, except in three participants (one each in IV, IM and SC groups); increases in mean arterial pressure (MAP) did not exceed 120% of baseline, with the exception of four participants (n=2, IV; n=2, IM).
Singh et al. 2016	ketamine i.v. Infusion (2-3/week/4 week	no clinically significant changes in laboratory tests, pulse oximetry, and ECG were observed during the study.
Daly et al. 2018	esketamine intranasal (twice/week)	most of the esketamine-treated participants manifested transient elevations in blood pressure (maximum mean change: systolic, 19.0 mm Hg; diastolic, 10.3 mm Hg) and heart rate (maximum mean change: 9.4 bpm) on dosing days; maximum blood pressure values were observed in most cases at 10 or 40 minutes after the dose (systolic: 199 mm Hg; diastolic: 115 mm Hg); elevated values typically returned to the value observed before dosing by 2 hours after the dose; dose effect was not observed for heart rate, although the greatest mean increases from baseline during both periods were observed in the 84-mg esketamine group.

CONCLUSIONS

Ketamine and esketamine demonstrate rapid antidepressant effect in TRD patients. The drug exhibits good overall tolerability profile. The unmet need for improved pharmacotherapies for TRD means the use of ketamine and esketamine is warranted therapeutic option in patients who fail to achieve a sustained remission of depressive symptoms with drugs with monoamine-based mechanisms of action. Adequate safety measures must be applied when using ketamine/esketamine in TRD subjects with particular focus on somatic comorbidities as the transient drug effect on cardiovascular system is demonstrated and of clinical significance. However, the evidence for its safety in TRD patients is strong with adequate treatment regimen being used.

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Contribution of individual authors:

Joanna Szarmach: study conception and design, acquisition of data, analysis and interpretation of data, drafting of manuscript.

Wiesław Jerzy Cubała: drafting of manuscript, critical revision.

Adam Włodarczyk: analysis and interpretation of data.

Mariusz S. Wiglusz: critical revision.

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