Therapeutic Advances in Psychopharmacology Case Report

Apnea during slow sub-anaesthetic infusion of intravenous ketamine for treatment-resistant depression

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***Abstract*:** Ketamine's pharmacological profile makes it an interesting and useful drug to challenge treatment-resistant-depression (TRD). Emerging adverse events associated with single-slow-sub-anaesthetic doses for the treatment of depression are common, although generally transient and self-limited. Nevertheless, data on the safety of this practice are scarce. Thus, it seems timely before ketamine is used for clinical treatment of depression to recommend careful monitoring and reporting of all potential adverse events related to ketamine administration. Here, we describe a case of apnea during slow sub-anaesthetic infusion of intravenous ketamine for the treatment of resistant depression. As far as we are concerned, this is an uncommon, previously unreported, and potentially severe adverse event that clinicians should be aware of, and specific management measures should be implemented.

Keywords: adverse events, apnea, ketamine, treatment-resistant depression

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Introduction

Major depressive disorder (MDD) is a common disorder, with a lifetime prevalence of 16.2% in the United States (US).[1] MDD is often a chronic and/or relapsing condition associated with a reduction of patient's functionality. This entails a huge personal, familiar, and social burden.[2]

MDD has been classically treated with drugs targeting the modulation of systems regarding monoamine neurotransmission. Two main mechanisms of pharmacologic action are used for this purpose. Either the blockade of noradrenaline, dopamine and/or serotonin reuptake by directly acting on their selective transporters, or the inhibition of monoamine breakdown by the monoamine oxidase enzyme.[3] Current antidepressants require between 4–6 weeks to achieve clinical improvement and around 50–70% of patients will achieve full recovery after the first episode.[4,5] Up to 20–30% of the remaining patients will show resistance to treatment. In addition, of those patients who recover completely from the first episode, around 40% will experience a relapse within the following 2 years, and, after the second episode, relapse rates increase up to 75% of patients.[2,5–7] Although there is a lack of a universally accepted operational definition of treatment-resistant depression (TRD), and its underlying pathophysiological mechanisms remain poorly understood, several authors suggest that the failure of two adequate dose-duration trials from different antidepressant classes in a current depressive episode represents an optimal cut-off point to identify patients with TRD.[8,9]

Thus, improvement of remission rates and shortening the latency period before onset of drug action remain clinical needs in MDD treatment. In recent years, ketamine, a dissociative anaesthetic agent, has become a promising candidate to produce a rapid-onset antidepressant effect in MDD, including TRD,[10–12] and has demonstrated a fast effect on reducing suicidal ideation.[13,14]

Current literature

Ketamine for TRD

Ketamine is a high-affinity, non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist whose antidepressant mechanism is complex and yet to be fully elucidated.[15] At low doses, ketamine might rapidly increase synaptic glutamate release and expression of the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor, and relieve inhibition of brain-derived neurotrophic factor (BDNF) synthesis.[16–19] Thus, ketamine's antidepressant mechanism is hypothesized to activate intracellular signaling pathways involving the mammalian target of rapamycin (mTOR), enhancing synaptogenesis in neurons and circuitry damaged as a result of stress or persistent depression.[20] Ketamine's poor oral bioavailability has made the intravenous (IV) route the preferred and most studied mode of administration, although not without drawbacks.[21] For instance, ketamine has shown transient efficacy, and IV ketamine treatment protocols usually consist of twice or thrice weekly infusions of subanesthetic doses of ketamine (0.5 mg/kg for 40–60 min). IV ketamine treatment protocols usually include a close follow up to assess the potential appearance of acute side effects (dissociation, headache, dizziness, emesis, etc.), risk of abuse, or possible long-term side effects (cognitive effects, cystitis, etc.).[22] Most frequently reported side effects have been mild, transient, occurring usually during or shortly after the first treatment sessions, and tending not to appear after recurrent administrations.[23] These inconveniences have led to the consideration of other routes of administration, such as the intranasal formulation. Esketamine, the S-enantiomer of ketamine, was recently approved by the US Food and Drug Administration (FDA) and the European Medication Agency (EMA) as an intranasal augmentation therapy to newly started antidepressant in TRD. Evidence from a randomized, double-blind clinical trial of repeated doses (either two or three times per week) of IV ketamine (0.5 mg/kg) in TRD showed a number needed to treat (NNT) response at week two of nearly two,[10] which is a substantial superiority in favor of the IV route for short-term efficacy compared with the intranasal formulation.[1] In this sense, it would be of interest to test the efficacy, safety, and tolerability of IV ketamine as maintenance treatment on the mid- and long-term follow up *versus* esketamine. The latter has already established maintenance efficacy,[24,25] and is much easier to administer, but much more expensive and not available in many countries.

Ketamine in anaesthesiology

Ketamine has proven to be a safe drug in different clinical scenarios for a long time, especially in paediatric populations.[15] However, dissociative and psychotomimetic adverse events are likely to occur in adult populations.[26] The appearance of these adverse events may explain the expansion of its illicit use in certain environments, and, under different doses and routes of administration, to its use in anaesthesiology.[27] Ketamine's pharmacological mechanism is completely different compared with other anaesthetic drugs. As a result, it may be considered in its own anaesthetic classification. Ketamine deploys its anaesthetic effect by disconnecting the limbic and thalamocortical systems.[15] In this way, the central nervous system dissociates from outer stimulation, and patients are unable to experience pain or any other perception like smell, sight, or sound. Consequently, the patient transitions to a trance-like cataleptic state called "sensory isolation".[15] The main advantage of this type of anaesthetic drug is its safety, since it is capable of maintaining cardiovascular stability, spontaneous breathing, and protective reflexes of the airway, while inducing powerful sedation-analgesia and amnesia.[28] Ketamine-related airway and respiratory adverse events are rare.[15] Subclinical respiratory depression and mild transient apnea (lasting less than 1 min) in children (there is a lack of data in adults) undergoing procedural sedation occur below 0.8% of cases.[29] Procedural sedation employs higher doses [around 1.0–1.5 mg/kg IV or 3–4 mg/kg intra-muscular (IM)] and infusions are administered much faster (within 1–2 min) than those used for ketamine antidepressant effect.[15,30]

Aim of this case report

Ketamine's pharmacological profile makes it an interesting and useful drug to challenge TRD. Emerging adverse events associated with single-slow-sub-anaesthetic doses for the treatment of depression are common, although generally transient and self-limited. Nevertheless, data on the safety of this practice are scarce. High doses and repeated administration have been associated with potentially serious and possibly persistent toxic effects both in patients treated for chronic pain and in people who use recreational ketamine.[27] These side effects include urological, hepatic, craving or dependence, and cognitive changes.[23] To date, these side effects have not been assessed adequately in studies investigating ketamine use in depression.[22] Almost all randomized controlled

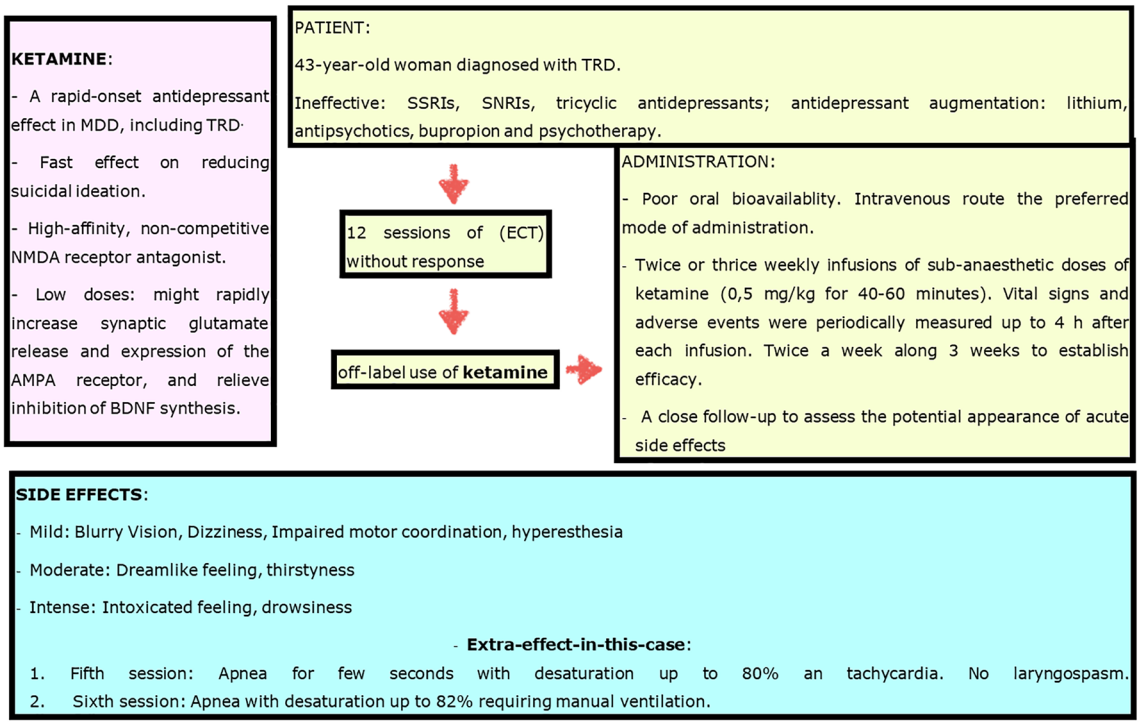

Figure 1. Summary of ketamine indication, administration, and side-effects, and patient case history.
AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; BDNF, brain-derived neurotrophic factor; ECT, electroconvulsive therapy; MDD, major depressive disorder; NMDA, N-methyl-d-aspartate; TRD, treatment-resistant-depression.

trials assessed the safety of single sessions of ketamine, but with only short term follow up. Long-term safety is, therefore, uncertain.[21] Thus, it seems essential before ketamine can be used for clinical treatment of depression, to recommend careful monitoring and reporting of all potential adverse events related to ketamine administration. We report on our experience of treating resistant depression with IV ketamine to share in the growing body of evidence concerning its safe use. We describe a case of apnea during slow sub-anaesthetic infusion of IV ketamine for the treatment of resistant depression. To our knowledge there is only one case report in which apnea was described after an infusion of a sub-dissociative dose of 25 mg of ketamine (0.31 mg/kg). In that case report, ketamine was used for sedation prior to preoxygenation, and the time of infusion was much shorter (around 20 s) than the usual schedule for antidepressant purposes. Just 1 min after the infusion, the authors described an abrupt apnoea episode without any respiratory effort or evidence of laryngospasm (another known adverse effect of ketamine).[31] As far as we know, there are no reported cases of apnea after slow infusions of sub-anaesthetic doses of ketamine for antidepressant use. This is an uncommon, unreported, and potentially severe adverse event that clinicians should be aware of and should ensure that specific management measures are in place in case of occurrence.

Case outline

Regarding the safety and tolerability of slow IV administration of low ketamine doses as a rapid-onset antidepressant augmentation, we present the case of a 43-year-old woman diagnosed with TRD (as assessed in a structured psychiatric interview) (Figure 1). The patient was healthy and did not suffer any physical comorbidity or require medication for physical conditions. The patient presented an index depressive disorder after the birth of her first child, at the age of 26 years. She fully recovered from that episode under selective serotonin reuptake inhibitors (SSRI) antidepressant treatment. At 35 years old, she relapsed and required a period of admission at our inpatient unit. After switching her antidepressant treatment to venlafaxine, she remitted from that episode and

Han grading scale for mask ventilation: scale for assessing the difficulty of ventilation with a face mask (Han et al., 2004)

- Han 0: Face mask ventilation was not attempted.
- Han I: Easily ventilated with a face mask.
- Han II: A supraglottic device was required for adequate ventilation.
- Han III: Difficult ventilation (unstable, needed help from another person).
- Han IV: Ventilation with face mask was not achieved.

Figure 2. Han grading scale for mask ventilation. Scale for assessing the difficulty of ventilation with a face mask.[34]

was able to reach recovery after titration to optimal doses and several months of treatment. At the age of 42, she presented with a new relapse. During her follow up, characterized by the persistence of severe depressive symptoms, after several changes of medication [three different antidepressants from different pharmacologic families including SSRIs, serotonin–norepinephrine reuptake inhibitors (SNRIs) and tricyclic antidepressants, lithium, and antipsychotic augmentation] combined with psychotherapy, she failed to reach remission. Pseudo-resistance was discarded after monitoring the intake of treatment and obtaining antidepressant levels in blood. Electroconvulsive therapy (ECT) was also carried out, and a lack of response was established after 12 sessions. In absence of further possible therapeutic resources at our disposal, the use of ketamine was proposed as a compassionate treatment, which required the drafting and approval by the department of pharmacy and hospital's ethics committee of a specific protocol for this clinical use. All IV ketamine infusions were supervised by a psychiatrist and an anesthesiolgist. The patient's written informed consent was the definitive requirement before initiating IV ketamine treatment.

IV ketamine therapy

Evidence provided from previous research,[11,32] suggested the choice of repeated administrations of IV ketamine at a dose of 0.5 mg/kg in physiological saline during 45 min twice a week for 3 weeks (i.e., a total of six sessions) to assess efficacy. Previous oral medication was sustained at fixed doses. Psychometric assessment included the Hamilton Depression Rating Scale (HAM-D).[33] Adverse events and vital signs (blood pressure, heart and respiratory rates, and oxygen saturation) were monitored within 4 h of treatment administration. The infusion and post-infusion process were attended by a nurse, a psychiatrist, and an anaesthesiologist. After 2 weeks of treatment, the patient experienced a reduction close to 50% on the HAM-D, and a score of 14, which was close to the proposed criteria for clinical response. Emergent secondary effects that far were dizziness, headache, paraesthesia, and nausea which appeared during the first two sessions and self-limited within 1–2 h after drug administration. However, during the fifth IV subanesthetic ketamine infusion session (0.5 mg/kg dose; body mass index: 24.22 kg/m^2 and a total dosage of 31 mg of IV ketamine), the patient presented a self-limited apnea episode lasting around 30 s with desaturation up to 80% and transient tachycardia, which solved spontaneously and did not require manual ventilation (HAN 0; Figure 2).[34] No signs of laryngospasm were observed. Despite this transient adverse event, the session completed without any other incident.

During the sixth session, the patient presented a new episode of apnea 25 min after the start of the ketamine infusion, with desaturation of up to 82% requiring manual ventilation (HAN II; Figure 2) with ambu and guedel placement by an experienced anesthesiologist, after which the patient recovered quickly to 100% saturation in less than 1 min. During the episode, she maintained hemodynamic stability and heart rate around 65 beats per minute (bpm) without other incidents. After having apnea episodes in two consecutive administrations, the medical staff, in accordance with patient preferences, decided to stop IV ketamine treatment in this patient.

Implications for clinical care

Our case report highlights the importance of acquiring greater experience regarding the use of IV ketamine to prevent uncommon, but potentially severe, adverse effects.

As stated previously, ketamine represents a distinct category among anesthetic drugs regarding its differential pharmacological mechanism. It is also completely different from other antidepressant drugs. Under its anesthetic use, rather than displaying the dose-response continuum observed with all other procedural sedation and analgesia agents, ketamine dissociation usually appears at a dosing threshold of approximately 1.0–1.5 mg/kg IV.[15] Unlike other anesthetic agents such as opioid, inhalation or sedative-hypnotic agents, the administration of additional ketamine does not result in a deeper or enhanced sedation after passing the dissociative threshold.[15] In anesthesia, dissociative sedation can be achieved readily by administration of a single IV or IM loading dose, and the need for titration, in contrast to other sedatives, is only to maintain the dissociative state over time.[15] The safety of ketamine lies, to a large extent, in the fact that, following the usual administration procedures and within the range of doses used commonly in anesthetic procedures, the amount of ketamine used will not generate alterations in the airway or depress the respiratory center.[35] Consequently, ketamine-induced apnea or respiratory depression are transient and rare in case of occurrence, and result frequently from rapid IV infusion. Typically, respiratory depression is invariably detected at the moment of peak levels in the central nervous system (i.e., 1–2 min after IV infusion).[36] In our case report, apnea appeared after several sessions under identical conditions. In both cases, it appeared after more than 25 min of slow and low-dose IV ketamine infusion, and resolved in less than 1 min. None of the episodes resulted in any damage to the patient. It is important to consider the fact that IV ketamine is an augmentation treatment for TRD, reserved for patients in which at least two previous antidepressant treatment attempts have failed. In consequence, few therapeutic options remain available if patients do not respond or do not tolerate ketamine. Despite the release of intranasal esketamine, IV ketamine remains the treatment with the highest efficacy for the acute treatment of TRD regarding clinical evidence, and it should be considered as a first-line choice for the approach to TRD and suicide risk,[1] especially in situations in which esketamine will be less accessible due to the increased costs associated with patent protection. Ketamine has a long trajectory in anesthesiology, but is still an emerging drug in psychiatry. Awareness of uncommon, and potentially severe, adverse events such as mild transient apnea that might seriously affect the safety of patients must be generated in untrained or non-familiarized personnel.

Conclusion

It would be necessary to provide professionally trained teams for the management and optimization of the safety and likeliness of success of IV ketamine therapy. It seems appropriate to consider safety as a priority when administering IV ketamine as an antidepressant treatment. Administering the infusion in facilities with optimal equipment and a multidisciplinary team with adequate knowledge concerning the existence and management of potential adverse events should be the rule.

Conflict of interest statement

The authors declare that there is no conflict of interest.

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Ethical statement and informed consent

Written informed consent for the publication of patient information was provided by the patient. This study did not contain human or animal trials and did not require an ethical board approval.

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