

Use of repeated intravenous ketamine therapy in treatment-resistant bipolar depression with suicidal behaviour: a case report from Spain

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Abstract: The rapidly-acting antidepressant properties of ketamine are a trend topic in psychiatry. Despite its robust effects, these are ephemeral and can lead to certain adverse events. For this reason, there is still a general concern around the off-label use of ketamine in clinical practice settings. Nonetheless, for refractory depression, it should be an indication to consider. We report the case of a female patient admitted for several months due to a treatment-resistant depressive bipolar episode with chronic suicidal behaviour. After repeated intravenous ketamine infusions without remarkable side effects, the patient experienced a complete clinical recovery during the 4 weeks following hospital discharge. Unfortunately, depressive symptoms reappeared in the 5th week, and the patient was finally readmitted to hospital as a result of a suicide attempt.

Keywords: antidepressive agents, bipolar disorder, depression, ketamine, suicide

Introduction

Ketamine, a noncompetitive antagonist of the N-methyl-D-aspartate (NMDA) subtype of excitatory amino acid receptor, is a dissociative anaesthetic agent [Krystal *et al.* 1994]. It is commonly handled in anaesthesiology due to its safety in various clinical conditions, being used more in the paediatric population [Green *et al.* 2011]. Nevertheless, its management in adult patients has been controversial based on dissociative and psychotomimetic side effects [Strayer and Nelson, 2008], a fact that has led to its popularity as a drug of abuse [Schifano *et al.* 2008].

The first study showing the antidepressant effects of ketamine was reported 15 years ago [Berman *et al.* 2000]. Since then, a substantial body of evidence has gradually accumulated, as evidenced by several recently published systematic reviews and meta-analyses [Caddy *et al.* 2013; Kishimoto *et al.* 2014; Fond *et al.* 2014; Coyle and Laws, 2015; Lee *et al.* 2015; McGirr *et al.* 2015; Romeo *et al.* 2015; Parsaik *et al.* 2015; Xu *et al.* 2016; Alberich *et al.* 2016]. In these, the rapid and robust antidepressant and anti-suicidal properties of ketamine

are highlighted, while there are warnings about its temporary effect and the methodological difficulties of double-blind trials [Aan Het Rot *et al.* 2012]. Consequently, the main objective of future research is to determine how best to sustain ketamine's efficacy. It has been established that repeated infusions achieve superior outcomes compared with a single infusion [Murrough *et al.* 2013; Shiroma *et al.* 2014; Rasmussen *et al.* 2013; Diamond *et al.* 2014; Singh *et al.* 2016; Cusin *et al.* 2016], but strategies for maintenance are still lacking. Therefore, despite the enthusiasm generated, the off-label use of ketamine is still not yet widespread in clinical practice for treatment-refractory depression (TRD). For example, at the time of writing only two case reports have been published in Spain. [Cortiñas-Saenz *et al.* 2013; Montes *et al.* 2015].

Case

Clinical background

A 45-year-old female patient with refractory bipolar depression (as assessed in a structured

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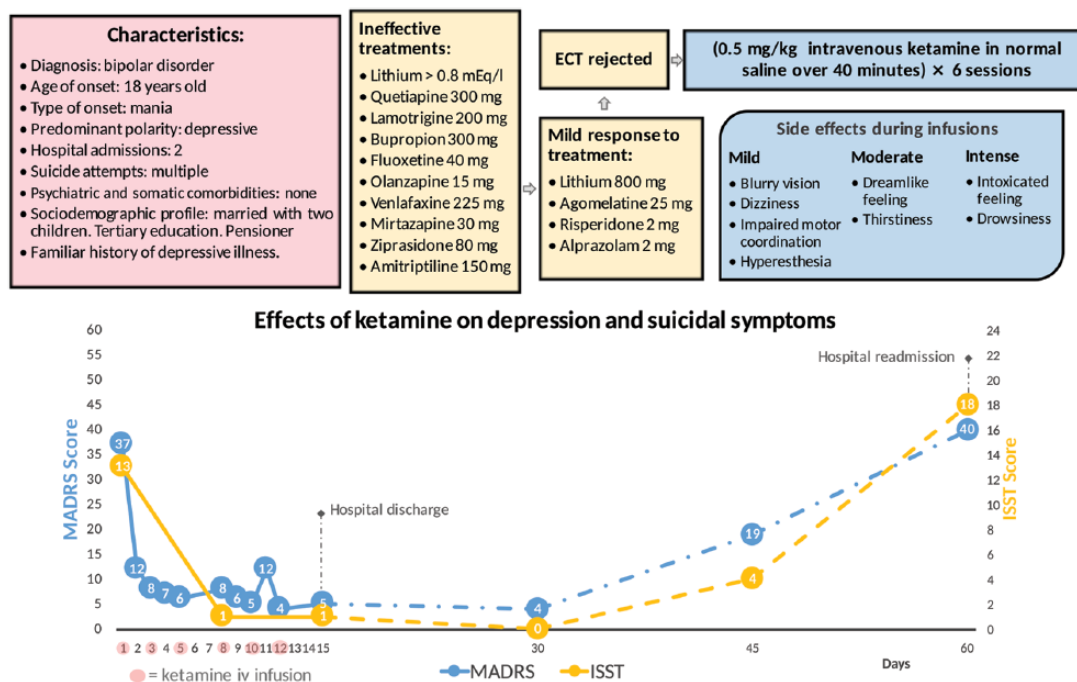


Figure 1. Effects of ketamine on depression and suicidal symptoms. ECT, electroconvulsive therapy; ISST, InterSePT Scale for Suicidal Thinking; MADRS, Montgomery-Åsberg Depression Rating Scale.

psychiatric interview) and chronic suicidal thoughts was admitted to care after an aborted suicide attempt at home. During admission, her evolution was underlined by the presence of major depressive feelings of hopelessness and intense anxiety levels that led the patient to exhibit recurring suicidal behaviour.

Several changes of medication (antidepressants, mood stabilisers and antipsychotics) and intensive programmes of psychotherapy were carried out, all of which were ineffective. A pharmacogenetic test (Neuropharmagen® AB Biotics, Spain) was conducted in order to identify the most suitable medication, with no findings of a specific profile in favour of certain psychotropic drugs. A lack of response to antidepressant treatment was established after a 4-week course at the doses recommended in the datasheet. Electroconvulsive therapy (ECT) was offered but rejected by the patient, citing stigma and side effects. Without further possible therapeutic resources at our disposal, and 6 months after her hospitalisation, the off-label use of ketamine was put forward. Authorisation was requested from the hospital's ethics committee, department of pharmacy and medical director, all approving the indication after a detailed technical report. With the informed consent of the patient and her relatives,

all ethical requirements were met, leading to the treatment then being initiated (see Figure 1).

Intravenous ketamine therapy

According to previously obtained evidence [Murrough *et al.* 2013; Shiroma *et al.* 2014; Rasmussen *et al.* 2013; Diamond *et al.* 2014], repeated administration was chosen, at a dose of 0.5 mg/kg of intravenous ketamine in normal saline over 40 min on Mondays, Wednesdays and Fridays over 2 weeks (i.e. six sessions in total). Previous oral medication was sustained at the same doses because, although it was ineffective for depressive symptoms, it was useful to treat anxiety, impulsivity and sleep disturbances. Psychometric assessment included the Montgomery-Åsberg Depression Rating Scale (MADRS) and the InterSePT Scale for Suicidal Thinking (ISST). Vital signs (blood pressure and heart rate) and side effects were periodically measured up to 4 h after each infusion.

Results

An impressive clinical response was registered just a few hours after the first session. In the following five infusions, this improvement was successfully consolidated, abating symptoms of

depression and suicide risk. At 2 weeks after the start of treatment, the patient was discharged from hospital and referred to outpatient psychiatric care. Euthymia was maintained for 4 weeks, in which the patient developed a functional recovery process. Unfortunately, this positive course was cut short in the 5th week, during which depressive symptoms abruptly reappeared until another suicide attempt brought about readmission to hospital (see Figure 1). In addition, it is notable that the episode remitted despite the fact that the patient was taking alprazolam. Recently, a number of authors have shown that benzodiazepines may attenuate the effectiveness of ketamine when administered concomitantly [Ford *et al.* 2015; Frye *et al.* 2015], although this interaction has been observed only in non-responsive patients.

With regard to side effects, these were confined to the period of ketamine infusion and were mainly of a sedative nature, disappearing entirely within the following 2 h. Neither psychotomimetic nor dissociative effects were recorded, as noted in several papers [Rasmussen *et al.* 2013; Diamond *et al.* 2014; Montes *et al.* 2015; Singh *et al.* 2016; Cusin *et al.* 2016]. Vital signs were also undisturbed (see Figure 1).

Discussion

The mechanism underlying the antidepressant effect of ketamine is complex and not yet well understood [Newport *et al.* 2015]. 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 [Romeo *et al.* 2015]. Furthermore, in animal models, ketamine activates the pathway involving the mammalian target of rapamycin (mTOR) and is conducive to synaptogenesis in neural circuits damaged due to chronic depression and stress [Li *et al.* 2010]. All these properties, which differ from the usual mechanisms of current antidepressants, place ketamine in a central role for the development of new interventions in TRD [Abdallah *et al.* 2015]. However, there is still caution over its use in clinical practice because of the risks of abuse and the occurrence of adverse effects (dissociative and psychomimetic) during administration although in this case report the patient did not present any notable side effect.

In the view of the authors, intravenous ketamine infusion is an intervention to be considered in hospital settings when patients with TRD have recurrent suicidal ideations. The next challenge is what to do when depressive symptoms return, which is the norm, as can be seen in this case report.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

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