NOTA CLÍNICA

A HOPEFUL ALTERNATIVE "THERAPY WITH INTRANASAL ESKETAMINE IN A PATIENT WITH RESISTANT DEPRESSION". A CASE REPORT

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Abstract. Major Depressive Disorder is the leading cause of disability worldwide. Treatment-resistant depression occurs in a subgroup of patients with this disorder, and consists of a lack of response to two or more different antidepressants under adequate doses and duration, with optimal adherence to treatment. In 2019, both the FDA and EMA approved intranasal esketamine for the treatment of Major Depressive Disorder, with a mechanism of action based on NMDA receptor antagonism. This article describes the case of a patient with Major Depressive Disorder treated with esketamine in compassionate use, the side effects experienced and their management. The results were spectacular: a very favourable clinical response was observed from the third administration, with complete remission seen at 5 weeks. It proved to be very effective with a great speed of action, and was the only antidepressant capable of achieving complete remission for this complex, severe patient, in addition to being able to reduce the concomitant medication. Side effects were easy to manage, transient and self-limiting at the time of administration. As described in the SmPC and the intranasal esketamine therapeutic positioning report, treatment must be administered in an appropriate clinical setting (either a hospital or as an outpatient), with the necessary resources for administration and subsequent observation of the patient.

Keywords. intranasal esketamine; esketamine nasal spray; treatment-resistant depression; dissociation; safety and efficacy

UNA ALTERNATIVA ESPERANZADORA "LA TERAPIA CON ESKETAMINA INTRANASAL EN UNA PACIENTE CON DEPRESIÓN RESISTENTE". A PROPÓSITO DE UN CASO

Resumen. El Trastorno Depresivo Mayor es la causa principal de discapacidad a nivel mundial. La depresión resistente al tratamiento ocurre en un subgrupo de pacientes con trastorno depresivo mayor, y consiste en una falta de respuesta a dos o más antidepresivos diferentes en dosis y duración adecuadas, con una adherencia óptima al tratamiento. En 2019 tanto la FDA como la EMA aprobaron la indicación de esketamina intranasal (esketamina in-) en el Trastorno Depresivo Mayor, cuyo mecanismo de acción se basa en el antagonismo del receptor NMDA. En este artículo exponemos el caso de una paciente con Trastorno Depresivo Mayor, que fue tratada con esketamina en uso compasivo, los efectos secundarios presentados y el manejo de los mismos. Los resultados fueron espectaculares, ya que, a partir de la tercera administración, se observó una respuesta clínica muy favorable, evidenciándose la remisión completa a las 5 semanas. El uso de esketamina intranasal ha demostrado ser muy efectivo y con una gran rapidez de acción, siendo el único antidepresivo capaz de lograr la remisión completa en esta paciente tan compleja y grave, además de conseguir ajustar a la baja la medicación concomitante. Los efectos secundarios fueron de fácil manejo, transitorios y autolimitados al momento de la administración. Tal y como se describe en la ficha técnica y en el informe de posicionamiento terapeútico de esketamina intranasal, el tratamiento debe ser administrado en un entorno clínico adecuado, que podría ser bien el hospital o el ambulatorio, ya que ambos contienen los recursos necesarios para la sesión de administración y posterior periodo de observación del paciente.

INTRODUCTION

Major depressive disorder is the leading cause of disability globally in relation to total years of life lost, and is associated with increased mortality (Popova *et al.*, 2019)

Treatment-resistant depression (TRD) occurs in a subgroup of patients with major depressive disorder and, according to the EMA definition, consists of a failure to

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respond to two or more different antidepressants under an adequate dose and duration, with optimal adherence to treatment. (European Medicines Agency, 2013)

Currently, there are limited therapeutic options for patients with TRD. Oral antidepressants take 5 to 8 weeks to take effect (Rush *et al.*, 2006) and around 60% of patients are on the same treatment for more than 220 days (Heerlein *et al.*, 2021). Each unsuccessful line of treatment is one more link in the chain of despair that this disease entails for these patients, their family members and healthcare professionals.

Both the US (FDA) and European (EMA) medical agencies approved the indication of esketamine for TRD in 2019. Esketamine is the S-enantiomer of racemic ketamine and is 1.5 to 4 times more potent against the NMDA receptor than ketamine or arketamine (Ebert *et al.*, 1997).

The mechanism of action of esketamine is based on NMDA receptor antagonism, which leads to the modulation of excitatory glutamate transmission and the release of BDNF, activating neurotrophin signalling and synaptogenesis (González-Pinto, 2020; Krystal *et al.*, 2002).

Classical antidepressants occasionally increase BDNF levels and require chronic activation through the second messenger system, producing indirect effects in terms of the number and function of dendritic spines. In particular, classical antidepressants do not produce an increase in glutamate, which is required for the release-dependent activity of BDNF. Synaptic protein levels, which presumably correlate with synapse formation, increase in the prefrontal cortex within 2 hours of ketamine administration (Li *et al.*, 2010; Gerard M *et al.*, 2016).

CLINICAL CASE

A 57-year-old woman, married with two children. Primary studies. Unemployed. 57% disability (due to mental illness). The 9th child from a family of 10. Several first-degree relatives with affective disorder symptoms.

She made her first psychiatric consultation in 2002 and was diagnosed with panic disorder and anxiety symptoms. She responded well to initial treatment with sertraline and alprazolam, and was discharged after 4 years of follow-up (in 2006).

She returned in 2013, after 4 years of follow-up in a private setting where she went after experiencing panic attacks and mild agoraphobia. She was initially treated with fluoxetine, topiramate and bupropion, to which she did not respond, and then paroxetine, topiramate and alprazolam, which partially improved her condition (milder and less frequent anxiety attacks).

During 2017, together with anxiety symptoms, she began to experience depression most of the day and almost every day; with decreased interest in activities that were previously pleasurable; difficulty in carrying out daily activities; increased weight; insomnia; psychomotor retardation; a lack of initiative and difficulty concentrating; and was thus developing symptoms compatible with an episode of major depression. Some improvement was seen after associating a tricyclic antidepressant (clomipramine) with an SSRI (paroxetine). However, a year later, she had a relapse, without triggers, which worsened over the following months, with reiterated thoughts of death appearing without structured autolytic ideation. On this occasion and throughout the following months, various antidepressants from the SSRI, SNRI and tricyclic families were used alone and in combination with each other and with antipsychotics, such as quetiapine, perphenazine and lurasidone. Improvement was seen with anxiety symptoms, but not with depressive ones. An improvement in the depressive symptoms occurred only when aripiprazole (10 mg) was added to treatment with fluoxetine (60 mg). However, this was withdrawn after experiencing akathisia-type side effects.

MAOIs were not given, as their use is not currently widespread; and the patient rejected electroconvulsive therapy (ECT) as too traumatic and stigmatising an approach.

Before starting treatment with intranasal esketamine, the patient was on venlafaxine (300 mg), alprazolam (1.5 mg), zolpidem (5 mg) and gabapentin (800 mg) daily (see Table 1). She also attended monthly psychotherapy sessions.

Figure 1 Patient psychiatric history.

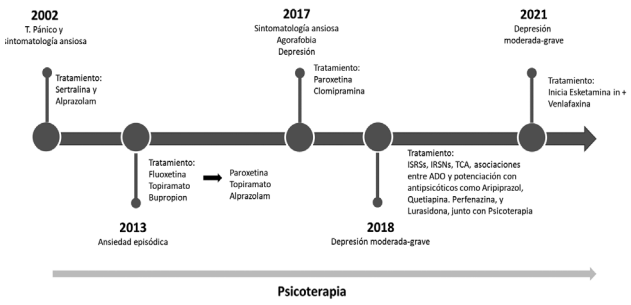
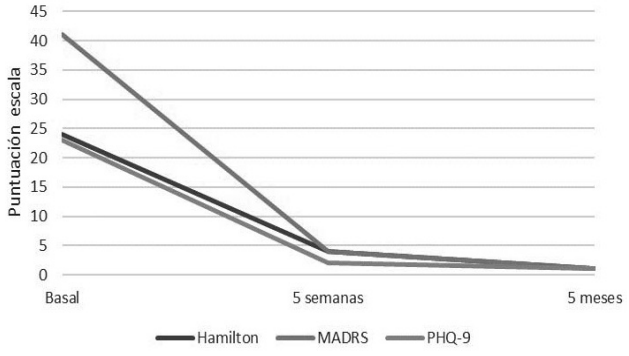


Table 1 Treatment prescribed for the patient before starting intranasal esketamine.

Class	Previous treatment
Antidepressants	Venlafaxine (300 mg/day)
Anxiolytics/Hypnotics	Alprazolam (0.5 mg/8 h), Zolpidem (5 mg)
Other psychoactive drugs	Gabapentin (400mg/12 h)

Given the lack of response to the different treatments used (see Fig. 2: HDRS=24, MADRS=41 and PHQ-9=23), treatment with intranasal esketamine began in July 2021 at the Infanta Margarita de Cabra Hospital, Córdoba, together with the concomitant medication described in Table 1. Treatment with intranasal esketamine was carried out prior to marketing through compassionate use, with agreement obtained from the AEMPS.

Figure 2 Evolution of depressive symptoms with the Hamilton Rating Scale for Depression (HDRS), Montgomery Asberg Depression Rating Scale (MADRS) and Patient Health Questionnaire (PHQ-9).



To achieve good tolerance with the first dose of intranasal esketamine, initial treatment was 28 mg (1 device), which led to a mild, self-limiting dissociative condition, from which the patient recovered 2 hours after administration. On the second day of administration, 56 mg (2 devices) was given, which led to the same mild, transient dissociative symptoms, which subsided with lorazepam (1 mg), with a transient, asymptomatic and slight increase in blood pressure. The induction dosage (56 mg/twice a week) was continued over the following days. Blood pressure were measured before administration of esketamine and 40 minutes afterwards; with the use of captopril established by protocol for a blood pressure higher than 140/90 (mmHg; systolic blood pressure, SBP, over diastolic blood pressure, DBP). This was required on three occasions: the first with a blood pressure (BP) of 160/95 (mmHg, SBP/DAP); the second with a BP of 155/95; and the third with a BP of 165/95. In addition, prior to treatment from the third dose, lorazepam (1 mg, sublingual) was administered in all sessions to calm the patient's nervousness over possible dissociation effects.

From the third administration, a notable clinical response was observed (HDRS=15 MADRS=24 and PHQ-=13) with complete remission at 5 weeks (Fig. 2. HDRS=4, MADRS=4 and PHQ-9 = 2). The patient showed her improvement by increasing her personal hygiene, going to the hairdresser, signing up for gymnastics and stating that her self-esteem and security had improved; with thoughts of death vanishing while feeling calm with an inner peace.

The maintenance regimen was continued and the concomitant medication was adjusted by reducing the venlafaxine dosage to 225 mg/day. After 12 weeks of treatment, due to the clinical stability and the euthymic status of the patient, the esketamine dose was reduced to 28 mg, with good tolerance. After 2 weeks of maintenance with 28 mg, a slight, transient and self-limiting (less than 2 weeks) worsening was reported, which did not require any farther intervention.

To keep the patient on the dosage indicated on the data sheet, it was decided to increase the intranasal esketamine dose to 56 mg every 15 days (2 devices). After 5 months with the treatment, the patient continued in euthymic status and reported feeling well and happy with the treatment, with objective maintenance of clinical efficacy (Fig. 2. HDRS=1, MADRS=1 and PHQ-9= 1).

CONCLUSIONS

We have described the case of a patient with a very severe recurrent major depressive disorder who had gone through successive lines of treatment and different therapeutic strategies without success. For this reason, treatment was tried with intranasal esketamine, restricted to a limited number of patients who meet the requirements within the framework of compassionate use. It proved to be very effective and very rapid acting; being the only antidepressant capable of achieving complete remission in this complex, severe patient, in addition to allowing concomitant medication to be reduced. Side effects were easy to manage, were transient and self-limiting at the time of administration, with the patient returning home

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normally after completion of the observation period. According to these results, intranasal esketamine may be a third therapeutic line with a good safety profile for the type of patients it is indicated for. It would thus be the first and only drug in Europe with an indication on the data sheet for patients with major depression who have failed at least 2 antidepressant treatments.

Treatment must be administered in an appropriate clinical setting, which is one that has the necessary resources (comfortable chairs and blood pressure monitor) and a qualified health professional to treat the patient during administration and provide subsequent monitoring.

ABBREVIATIONS

- FDA: Food and Drug Administration.
- EMA: European Medicines Agency
- OAD: Oral antidepressant
- AEMPS: Spanish Agency for Medicines and Medical Devices
- TRD: Treatment-resistant depression
- in: Intranasal
- SSRI: Selective Serotonin Reuptake Inhibitor
- SNRI: Selective serotonin and norepinephrine (or noradrenaline) reuptake inhibitor
- NMDA: N-methyl-D-aspartate

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