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RAPID COMMUNICATION

Antidepressant, mood stabilizing and procognitive effects of very low dose sublingual ketamine in refractory unipolar and bipolar depression

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Abstract

Intravenous ketamine (0.5 mg/kg) produces robust, rapid and long-lasting antidepressant effects, but is unpractical. Sublingual administration of ketamine renders better bioavailability (~30%) and less conversion to norketamine than oral administration. We evaluated the therapeutic effects and tolerability of very low dose sublingual (VLDS) racemic ketamine (10 mg from a 100 mg/ml solution for 5 min and swallowed), repeatedly administered every 2–3 d or weekly, in 26 out-patients with refractory unipolar or bipolar depression. According to patients' reports, VLDS ketamine produced rapid, clear and sustained effects, improving mood level and stability, cognition and sleep in 20 patients (77%), with only mild and transient light-headedness as a common side-effect (no euphoria, psychotic or dissociative symptoms). Remission remained in some patients after stopping ketamine. Thus, VLDS ketamine may have broad spectrum effects beyond its antidepressant properties, with rapid onset of action, high efficacy, good tolerability and low cost, allowing extended treatment as needed.

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Key words: Antidepressant, depression, ketamine, mood stabilizer, sleep.

Introduction

The rapid antidepressant effect of a single sub-anaesthetic i.v. dose of ketamine is one of the most significant conceptual breakthroughs in the pharmacological treatment of depression. Response to this NMDA receptor antagonist takes place within a few minutes of administration in 55–80% of subjects and may last up to 7–10 d. These robust, rapid and long-lasting effects of a single dose of i.v. ketamine (0.5 mg/kg) have been well documented in small controlled clinical trials for major depression (Berman et al., 2000; Zarate et al., 2006; Valentine et al., 2011) and bipolar depression (DiazGranados et al., 2010; Zarate et al., 2012). Also, in selected cases the repeated i.v. administration of ketamine every 2–3 d was effective (Aan Het Rot et al., 2010; Murrough et al., 2012), suggesting that tolerance to its antidepressant effects does not develop. One strategy aiming to maintain the acute antidepressant effect of i.v. ketamine in a feasible way was to switch to oral treatment with the glutamatergic modulator Riluzole, which was ineffective in two placebo controlled studies (Mathew et al., 2010; Ibrahim et al., 2012).

Despite this conceptual advance, the need to submit patients to i.v. administration within a hospital setting is a strong limitation for a more widespread and continuous administration of ketamine. Thus, the application and maintenance of ketamine treatment depends on finding better routes of administration than i.v. Intramuscular injection at ~1 mg/kg was efficacious in five case reports (Glue et al., 2011; Cusin et al., 2012; Zanicotti et al., 2012), but is far from ideal. Ketamine after oral administration undergoes rapid first pass metabolism, resulting in only 17% bioavailability and high conversion to the metabolite norketamine (Clements et al., 1982), but there are three case reports of successful treatment with 0.5 mg/kg oral ketamine in patients receiving hospice care (Irwin and Iglewicz, 2010; McNulty and

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Table 1. Clinical characteristics and response to VLDS ketamine in patients with MDD, recurrent MDD (with or without cyclothymic disorder), bipolar II and bipolar I disorder

Patient/ gender/ age (yr)	Psychiatric diagnoses	Duration of actual episode (months)	Previous episodes	Previous pharmacological treatments	Ketamine posology (each dose is 10 mg sublingual)	Clinical outcome
1/F/36	Dysthymia, recurrent MDD	3	4	Nortriptiline, sertraline, lamotrigine fluoxetine, venlafaxine, sulpiride, trazodone, citalopram*	Every 3 d, 12 doses	Rapid and sustained increase in energy, motivation, resilience, vigour and pleasure.
2/M/64	MDD, chronic pain	28	3	Trazodone*, divalproate*, lamotrigine, gabapentine, nortriptiline, 3 SSRIs	Every 2 d, continuous treatment	Rapid and sustained response to depressive symptoms, but no benefit for chronic pain.
3/F/35	Recurrent MDD, previous panic attacks	6	4	Fluoxetine, paroxetine, lamotrigine, clonazepam*, venlafaxine*, topiramate*	Every 2 d, 18 doses	Rapid increase in motivation and resilience to go through family problems; sustained response after stopping ketamine.
4/F/79	MDD	35	1	Citalopram*, mirtazapine, venlafaxine, paroxetine	0.5 dose (elderly) every 2 d, 10 doses; continuous treatment weekly	Rapid and sustained response, caregiver asked 'what happened to you that you are so well?' the day after the first dose. Remission maintained with 1 drop/wk, which was requested by the family.
5/F/36	MDD	6	3	Sertraline, escitalopram, bupropion*, methylphenidate*, duloxetine*	Every 3 d, 4 doses	Gradual response over 3 d, with improved energy, cognition, frustration tolerance, ability to communicate and sleep.
6/F/77	Recurrent MDD, chronic depression, chronic insomnia	96	5	Quetiapine, escitalopram, venlafaxine, amisulpride, lithium*, alprazolan*, modafinil*, duloxetine*	Every 3 d, 5 doses	Gradual response over a few days in motivation, energy, mental agility and sleep; started regular walks spontaneously.
7/M/38	Recurrent MDD and GAD	2	4	Fluoxetine, sertraline, duloxetine, paroxetine, paroxetine CR*, clonazepan*	Every 3 d, 5 doses	Rapid response in depression and anxiety after first dose. Improved sleep.
8/F/57	*Recurrent MDD, chronic depression*	*10*	*>10*	*Escitalopram, sulpiride, mirtazapine, lamotrigine*, gabapentine, trazodone, T4*	*Every 2 d, 12 doses up to 0.25 ml*	*Rapid but only moderate and transient improvement (<24 h) after each dose. Interrupted due to unsatisfactory response.*
9/F/36	*Recurrent MDD, refractory to ECT*	*8*	*5*	*Venlafaxine*, lamotrigine, quetiapine, 3 SSRIs, T4, MAO inhibitor*	*Every 3 d, 8 doses; sublingual dose increment and i.v.*	*Slight improvement from adverse events of recent ECTs (some confusion and 'strange' feeling). No further improvement with higher doses (up to 8 drops) or i.v. 0.5 mg/kg ketamine in hospital.*

10/F/45	MDD, cyclothymic disorder, PTSD	12	3	Lithium, desvenlafaxine, divalproex, fluoxetine, topiramate, lamotrigine*, oxcarbazepine*	Every 2 d, 8 doses	Rapid response after first dose, improved energy and emotional regulation. Transient tachycardia (<30 min) after ingestion.
11/M/69	MDD, Cyclothymic disorder, chronic insomnia	2	5	Fluoxetine, bupropion, oxcarbazepine, methylphenidate, trazodone, venlafaxine, duloxetine, psychotherapy, lamotrigine*.	Every 2 d, 4 doses	Rapid response after first dose, increased motivation, mood stability and improvement of sleep quality.
12/F/83	Recurrent MDD, cyclothymic disorder, chronic depression	36	7	Quetiapine, mirtazapine*, clonazepan*, escitalopram*, methylphenidate*, olanzapine*, duloxetine*	Single dose	After single dose, sustained response (around 70% according to her) in energy, hope, motivation, sleep and physical complaints.
13/M/22	Bipolar II, Internet addiction	3	3	Fluoxetine, olanzapine, lithium, divaploate*, quetiapine*, lamotrigine*	every 3 d, 8 doses	Rapid and sustained response, remission from depressive symptoms from the 2nd dose onwards, sustained response after stopping ketamine
14/F/26	Bipolar II, depressive episode	4	7	Quetiapine*, topiramate, fluoxetine, aripiprazole, oxcarbazepine, lithium, divalproex, paroxetine	Every 3 d, 18 doses	More active, alert, stable and motivated with ketamine, improved sleep, sustained response after stopping ketamine
15/F/24	Bipolar II, chronic depression	56	5	Lithium, olanzapine, 3 SSRIs, bupropion, quetiapine, sulpiride, aripiprazole, lamotrigine, trazodone, ketoconazole* methylphenidate, T4, θ3,	Every 2 d, continuous treatment for ~5 months	Rapid but only moderate improvement in motivation; only drug yielding benefit in the last 4 yr. Some further benefit with ketoconazole later. Very sensitive to side-effects of mood stabilizers.
16/F/28	Bipolar II, depressive episode	3	3	Lamotrigine*, divalproex*, acetylcysteine*, oxcarbazepine, 2 SSRIs, methylphenidate	Every 2 d, 12 doses; 2 months later, >10 doses	Rapid and robust response; 'Became myself again', symptoms relapsed after stressful events; new course of treatment with response again
17/F/51	Bipolar II, ADHD, mixed depression with ultradian cycling	12	5	Quetiapine*, venlafaxine, oxcarbazepine, bupropion, lamotrigine, methylphenidate	Every 3 d, 12 doses	Rapid resolution of depression and ultradian cycling. Remission maintained after stopping ketamine. Improved sleep.
18/F/38	Bipolar II, previous cocaine dependence (abstinence >2 yr)	2	5	Risperidone, oxcarbazepine* topiramate, bupropion*, quetiapine*, citalopram	Every 3 d, 12 doses; continuous treatment ~6 months	Rapid increase in motivation, stability and resilience to go through family problems; low mood 3 wk after stopping ketamine; response returned and continued with weekly treatment.
19/F/46	Bipolar II, chronic insomnia, complicated bereavement	2	5	3 SSRIs, imipramine, bupropion, fluvoxamine, reboxetine, lithium, carbamazepine, lamotrigine*, quetiapine, oxcarbazepine, escitalopram	Every 2 d, 10 doses	Rapid response of all depressive symptoms and significant improvement of insomnia; more resilient regarding the bereavement. Remained well only on lamotrigine.

Table 1 (*cont.*)

Patient/ gender/ age (yr)	Psychiatric diagnoses	Duration of actual episode (months)	Previous episodes	Previous pharmacological treatments	Ketamine posology (each dose is 10 mg sublingual)	Clinical outcome
20/M/26	Bipolar II, depressive episode	3	5	Carbamazepine, topiramate, paliperidone, topiramate, venlafaxine, duloxetine, nortriptiline, gabapentine, 3 SSRIs, methylphenidate , oxcarbazepine, lithium, divalproex, aripiprazole*, bupropion*	Every 7 d, 20 doses	Clear reduction of depressive symptoms, irritability and excessive food intake; more 'rational' decision making, improved cognition and mood stability. Remains well after stopping ketamine.
21/F/34	Bipolar II, depressive episode	3	3	Divalproex, oxcarbazepine, methylphenidate, aripiprazole*, fluoxetine*, desvenlafaxine*	Single dose	Sustained remission after single dose, with recovery of energy, vigour, emotional regulation and adequate decision making.
22/M/50	Bipolar II, panic attacks, previous cocaine dependence (abstinence 2 months), chronic insomnia	5	12	Escitalopram, methylphenidate OROS, alprazolan, topiramate, mirtazapine*, duloxetine*, fluoxetine*, bupropion*, lisdexanphetamine*, quetiapine*	Every 3 d, 5 doses	Rapid, but moderate response, with partial improvement in energy, negative thinking, mood instability and cognitive dysfunction. Mild improvement in insomnia.
23/F/50	Bipolar II, GAD, past panic attacks	3	6	Quetiapine*, lamotrigine* oxcarbazepine, bupropion, 2 SSRIs, clonazepam	Every 3 d, 3 doses	Rapid and moderate improvement; increased anxiety after 3rd dose made her stop ketamine, but even so, remained somewhat better.
24/F/58	*Bipolar II, first episode of agitated depression*	*6*	*1*	*Lamotrigine*, quetiapine*, mirtazapine, venlafaxine*	*Single dose*	*No response. Later remitted with 15 mg olanzapine+40 mg fluoxetine. Referred numbing of the mouth during sublingual intake.*
25/M/30	Bipolar I, mixed depression	7	5	Lithium, divalproex, citalopram, quetiapine, methylphenidate, fluoxetine, escitalopram*, duloxetine, lisdexamphetamine*, aripiprazole*	Every 7 d, continuous treatment for ~4 months	Moderate, but sustained response with continuous treatment. Less mood swings, impulsivity and irritability. Gradual improvement in sleep and suicidal ideas.
26/M/38	Bipolar I, mixed depression	4	9	Divalproex*, quetiapine*, sertraline, oxcarbazepine* methylphenidate*, bupropion, venlafaxine*, fluoxetine, lamotrigine	Every 2 d, continuous treatment for ~6 months	Rapid but only moderate improvement in motivation and energy.

VLDS, Very low dose sublingual; MDD, major depressive disorder; F, female; M, male; GAD, generalized anxiety disorder; SSRIs, selective serotonin reuptake inhibitors; ECT, electroconvulsive therapy; MAO, monoamine oxidase; PTSD, post-traumatic stress disorder; ADHD, attention-deficit and hyperactivity disorder.

* Denotes ongoing treatments.

Text shown in italics indicates those with unsatisfactory response.

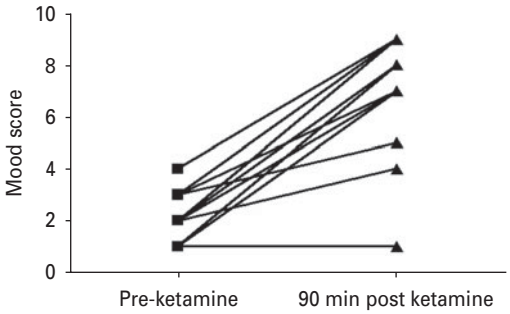

Fig. 1. Acute effects of very low dose sublingual ketamine administered sublingually (10 mg for 5 min to absorb) on subjective mood state in 11 patients with a depressive episode with poor response to at least four pharmacological treatments. Mood state was rated by the patient from 0 (very sad/negative/anergic/distressed) to 10 (very cheerful/positive/lively/peaceful) 90 min after the first ketamine dose.

Hahn, 2012) and two with refractory depression (Paslakis et al., 2010). Another alternative undergoing clinical trials (Aan Het Rot et al., 2012) is the use of a nasal spray, which renders a bioavailability of 45% (Yanagihara et al., 2003). However, ketamine in the usual liquid form is not friendly to use intranasally and may produce erratic absorption. Surprisingly, the sublingual administration of ketamine has not been explored but renders ~30% bioavailability and less conversion to norketamine than oral administration (Yanagihara et al., 2003). This route can be easily used with liquid ketamine and allows providing a small amount (~1 ml) to the patient in a dropper bottle to facilitate personal use while guaranteeing that the patient does not have access to a dose that can lead to anaesthesia or psychosis. Moreover, sublingual administration of drugs has been increasingly used for psychiatric drugs and is usually well accepted by patients.

Another issue that has been poorly studied is the dose–response curve for the antidepressant effects of ketamine. Since the original description used an i.v. infusion of 0.5 mg/kg ketamine over 40 min (Berman et al., 2000), most studies have just repeated the same protocol, but this dose selection was based on a serendipitous observation in a challenge study in depressed patients (Berman et al., 2000). Although this is considered a subpsychotomimetic dose, perceptual disturbances, drowsiness, euphoria, feeling 'strange', confusion and dissociation often occur in this dose (DiazGranados et al., 2010; Aan Het Rot et al., 2012). The reported efficacy of 0.5 mg/kg oral ketamine, which would lead to a bioavailability of ~6 mg in a 70 kg subject, suggests that the habitual i.v. dose of 0.5 mg/kg (bioavailability of 30–35 mg in a 70 kg subject) is more than is actually necessary.

With these considerations in mind, we started evaluating the effects and tolerability of very low dose sublingual (VLDS) ketamine administered in outpatients with unipolar or bipolar refractory depressive episodes.

Method

This study was conducted as an unsystematic case series in a clinical setting in patients who were explained about the procedures and provided written informed consent. This form was elaborated to fulfil the requirements of the National Health Council of Brazil (Resolution 196/1996) and the Code of Ethics of the World Medical Association (Declaration of Helsinki). This was a preliminary and exploratory evaluation conducted to establish new parameters of ketamine administration (dose, route, dose interval) to carry out a systematic clinical study. Patients included in this case series had to fulfil the DSM-IV criteria for major depression (single episode or recurrent) or bipolar disorder experiencing a depressive episode. They had to have unsatisfactory response to at least four pharmacological treatments indicated for their disorder, alone or in combination, for at least 4 wk at standard therapeutic doses.

Our strategy was to start with a very low dose (0.1 ml=2 drops) of racemic ketamine 100 mg/ml (i.e. 10 mg) administered sublingually, allowed to absorb for 5 min and swallowed. We then observed for acute therapeutic effects and increased the dose by 1 drop as needed in further doses on another day. Estimating the 30% bioavailability for this route, only 3 mg ketamine would be actually delivered at this starting dose, which is about 10 times lower than ~35 mg in a 70 kg subject undergoing the classical i.v. administration of ~0.5 mg/kg (~93% bioavailability) of previous studies. Then we considered the interval every 2–3 d or weekly, since its therapeutic effect tends to last for 2–7 d in most patients according to the literature and our initial observations. Maintenance of previous treatments was according to the evaluation of the psychiatrist in charge of the case, but no other medication was introduced simultaneously. Acute effects were assessed 90 min after the first ketamine dose in 11 patients with the question 'how is your mood right now?' with the possibility of giving a score from 0 to 10. Patients were instructed that 0 corresponds to being very sad/negative/anergic/distressed and 10 corresponds to being very cheerful/positive/lively/peaceful.

Results

Table 1 shows the clinical characteristics of patients treated with VLDS ketamine. Out of 26 patients, 20 achieved remission or clear response for depression, mood instability, cognitive impairment and poor sleep. Three patients had moderate or partial response and three failed to respond. Some patients or their relatives spontaneously used adjectives such as 'sensational', 'amazing', 'incredible' and phrases such as 'I am back to life again' and 'the best night of sleep in years' to describe the observed effects. Many reported to feel potent and confident again, but without the feeling of being under the effects of psychostimulants. No manic, psychotic or dissociative symptoms were observed, but two bipolar patients reported agitation for a few hours. Mild light-headedness was a common but transient side-effect, subsiding typically in <30 min and more pronounced or present only after the first dose.

Figure 1 shows the acute response to VLDS ketamine in 11 of these patients with a depressive episode (five unipolar, six bipolar), with eight patients reporting a clear response after the first dose.

Discussion

Our clinical observations were that VLDS ketamine produced rapid and robust effects on mood, sleep and cognition in around 75% of patients, with very good tolerability in most cases. The effect on sleep was often reported as remarkable for inducing a deep and repairing sleep, in line with previous findings of increased slow wave sleep by ketamine injection (Duncan et al., 2012). Also, some patients retained their therapeutic response even after stopping ketamine treatment, which may be associated with the strong neuroplastic changes produced by ketamine, as shown in animal studies (Duman and Aghajanian, 2012), but longer and more systematic observations are necessary.

These therapeutic benefits of VLDS ketamine in most patients with refractory depressive episodes resemble the descriptions of i.v. ketamine, but with better tolerance, ease of use and safety regarding psychiatric adverse events, allowing prolonged and even continuous treatment at home. Regarding clinical safety, no major complications have been reported with ketamine infusion (Aan Het Rot et al., 2012). It is considered safe clinically as an anaesthetic and the effect of repeated treatment in patients with pain have not reported major clinical complications at higher doses than the one used here (Blonk et al., 2010; Noppers et al., 2010).

This is a preliminary exploratory study in a clinical setting with clear limitations. These include the lack of a standardized diagnostic instrument and scales to evaluate psychiatric symptoms and adverse events, the use of unsystematic dose intervals and the inclusion of both unipolar and bipolar patients, many of them with co-morbidities. Thus, the therapeutic effects were evaluated solely on the reports of patients and relatives.

These clinical observations suggest new approaches to design randomized clinical trials, preferably with an active placebo (e.g. benzodiazepine) and evaluating aspects other than depressive symptoms (e.g. mood stability, cognition). If the therapeutic effects are confirmed, VLDS ketamine may become a much more convenient strategy than moderate dose i.v. treatment, allowing its use in a wider range of patients and settings. More studies will also be needed to establish the length of treatment (short term, long term), optimal interval between doses and to better characterize its safety and tolerability.

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Statement of Interest

None.

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