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Combination of intravenous S-ketamine and oral tranylcypromine in treatment-resistant depression: A report of two cases

KEYWORDS
Ketamine;
Tranylcypromine;
Monoamine-reuptake inhibition;
Irreversible monoamine oxidase inhibition;
Treatment-resistant depression

Abstract
Ketamine, a rapid-acting antidepressant and anti-suicidal agent, is thought to increase brain monoamine levels by enhancing monoamine release or inhibiting presynaptic monoamine-reuptake. Here we present two female inpatients suffering from treatment-resistant depression with recurrent severe suicidal crises receiving a combination of intravenous S-ketamine and oral tranylcypromine, which is a well-known irreversible monoamine oxidase (MAO) inhibitor. Since inhibition of monoamine-reuptake with concurrent blockade of MAO might trigger sympathomimetic crisis, this combination is considered hazardous. Nonetheless, cardiovascular parameters remained stable in both patients, while good anti-suicidal effects were observed. Hence, we put serious doubt on whether monoamine-reuptake inhibition is a relevant pharmacological effect of ketamine in humans.

1. Introduction

Ketamine is increasingly used as a rapid-acting antidepressant and anti-suicidal agent (Blier, 2013). Besides well-described antagonist actions at glutamatergic N-methyl-$_D$-aspartate receptors, ketamine has significant sympathomimetic properties used for treating conditions like bronchospasm in emergency-medicine settings. *In-vitro* and *ex-vivo*, ketamine was shown to increase brain monoamine levels by enhancing monoamine release or inhibiting presynaptic monoamine-reuptake (Tso et al., 2004; Nishimura and Sato, 1999).

Here we present two female inpatients suffering from treatment-resistant depression (TRD), who were treated with oral tranylcypromine, and who additionally received intravenous S-ketamine in the course of acute and severe suicidal crises. Since inhibition of monoamine-reuptake with concurrent irreversible blockade of monoamine oxidase (MAO) might trigger sympathomimetic crisis, this combination is considered hazardous.

2. Case-report

First we present a 43-years-old female patient (120 kg), who failed several antidepressant treatments, including selective and non-selective monoamine-reuptake inhibitors, tricyclic antidepressants, augmentation with antipsychotics, lithium, and thyroxin, sleep deprivation, bright light-, electroconvulsive- as well as cognitive-behavioral-therapy. Eventually, a combination of tranylcypromine and lithium reduced depressive symptoms for several months. However, tranylcypromine was discontinued for two weeks because of elective surgery requiring general anesthesia. After reinstating tranylcypromine 10 mg p.o. q.d., she became acutely suicidal again. Since S-ketamine (25–75 mg) led to good anti-suicidal effects in her history, intravenous S-ketamine 12.5 mg was slowly administered under cardiovascular monitoring. We observed good anti-suicidal effects, while no relevant changes in vital signs occurred during and after S-ketamine infusion. Hence, intravenous S-ketamine was gradually increased up to 75 mg, and was administered repeatedly. Concurrently, tranylcypromine was increased to 80 mg p.o.q.d. under plasma level monitoring.

Our second case, a 74-years-old female patient (59 kg) had also failed multiple antidepressant treatment attempts including tranylcypromine 20 mg p.o.q.d. Based on our previous experience with a safe concomitant administration of high-dose tranylcypromine and S-ketamine, she received intravenous S-ketamine 25 mg while acutely suicidal. Similarly, cardiovascular parameters remained stable during and after S-ketamine infusion. Since we observed good anti-suicidal effects lasting approximately one day, S-ketamine up to 50 mg/infusion was administered twice a week. Despite concomitant antidepressant

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treatment with tranylcypromine 20 mg p.o.q.d., Graves' disease as somatic comorbidity, and rather advanced age, no relevant cardiovascular changes occurred.

3. Discussion

To our knowledge, this is the first report on a combined antidepressant treatment with S-ketamine and tranylcypromine at low- and higher doses in humans. Since ketamine is thought to inhibit monoamine-reuptake (Tso et al., 2004; Nishimura and Sato, 1999), the combination with tranylcypromine should lead to increased blood pressure and heart rate. In both cases, we did not observe any relevant changes in these parameters. This corresponds with previous literature reporting no relevant cardiovascular or hemodynamic changes in a patient receiving tranylcypromine 20 mg p.o.q.d., who underwent anesthetic induction with ketamine 1.5 mg/kg (Doyle, 1990). Although it is impossible to generalize from three single reports, these observations put serious doubt on whether monoamine-reuptake inhibition is a relevant pharmacological effect of ketamine in humans. This assumption is further underlined by previous pre-clinical evidence showing that administration of 400 or 600 mg ketamine/kg body weight did not increase mortality in mice pretreated with tranylcypromine (Bruce and Capan, 1983). Furthermore, our safe experience might encourage researchers to investigate ketamine in combination with other antidepressant agents as treatment option in TRD.

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