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Ketamine's rapid antisuicidal effects are not attenuated by Buprenorphine

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ABSTRACT

Ketamine's rapid antisuicidal action has gathered significant clinical interest in treatment of depression though concerns exist that its actions occur through the Opioid pathway. A recent study additionally reported that Naltrexone blocks antisuicidal effects of Ketamine suggesting that its antisuicidal effects are also due to opioid mechanisms. We present a case of treatment refractory depression with recent suicide attempt and active suicidal ideations who was on an Opioid partial agonist, Buprenorphine, for management of pain. Patient responded to a trial of IV ketamine treatment with rapid improvement in suicidal thoughts. Patient's suicidal ideations decreased after first Ketamine treatment and resolved after second treatment while maintained on Buprenorphine. Our finding shows that Buprenorphine does not block Ketamine's effects on suicidal ideations and therefore Ketamine treatment could be provided safely in controlled environment to those with substance use disorders or with chronic pain while being maintained on Buprenorphine. Additionally, our case suggests that non-Opioid mechanisms may be involved in Ketamine's antidepressant effects and its response to suicidal ideations in those on Opioid partial agonists.

1. Introduction

Ketamine, a noncompetitive antagonist of the glutamatergic NMDA receptor, has gathered significant clinical interest due to its ability to act as a rapidly acting antidepressant (RAAD) and in its efficacy in treatment resistant depression (TRD) (Abdallah et al., 2015). Although the exact mechanism of action for Ketamine is not known, suggestions that Opioid pathways may mediate the antidepressant effects has raised concerns that Ketamine may pose risk of dependence and abuse (Williams et al., 2018). While a report indicated that antidepressant response occurs in patients on Opioid antagonist (Yoon et al., 2019), a more recent study found that Naltrexone attenuates Ketamine's antisuicidal response suggesting Opioid pathways are involved in antisuicidal response as well (Williams et al., 2019). We present a case of a patient with severe TRD who showed rapid improvement in suicidal ideations following initiation of IV Ketamine treatment despite being on maintenance therapy with buprenorphine/naloxone (BPN) combination, a Mu opioid receptor (MOR) partial agonist.

2. Case

Mr. L is a 40 year old Caucasian male veteran with history of major depressive disorder, post-traumatic stress disorder, chronic pain and psychogenic non-epileptic seizures referred to neuromodulation clinic at the Ann Arbor VA for management of worsened depressive symptoms. In the weeks leading to referral, he had been psychiatrically hospitalized at an outside hospital following a suicide attempt via intentional overdose with Opioid medications. Due to recent suicide attempt and to reduce risks of overdose patient was switched to BPN for pain management. After stabilization on the inpatient unit, patient was stepped down to partial hospital program which was truncated due to COVID 19 pandemic. During the follow up appointment with his outpatient provider patient screened positive on the Columbia-Suicide Severity Rating Scale triage screener. Upon a comprehensive suicide risk evaluation he reported active suicidal ideation with thoughts of overdosing and some intentions to act. He, however, denied any planning and meaningfully engaged in safety planning such that he could remain in treatment in the outpatient setting. With a Montgomery-Äsberg Depression Rating Scale (MADRS) score of 36, suicide subscale score of 4 with nearly daily suicidal thoughts and treatment resistance in the form of ten previous antidepressant or augmentation trials, the clinical team determined that he met criteria for ECT or Ketamine treatment. The patient expressed a preference for a trial of IV Ketamine treatment. Due to ongoing hold on IV Ketamine infusions due to COVID-19 pandemic, the patient was followed q2weeks with aripiprazole augmentation along with his existing outpatient medication regimen of duloxetine 120 mg qday, topiramate 200 mg BID, BPN 8/2 mg TID, melatonin 3 mg po qhs over 7 week period during which time he showed no improvement. After resumption of Ketamine services, Mr. L was started on IV Ketamine infusions twice a week dosed at 45 mg (0.5 mg/kg) IV infusion over 40 min duration while he also continued taking BPN 8 mg TID, which was confirmed by an urine buprenorphine screen. Patient reported rapid improvement in his suicidality and depressive symptoms by second Ketamine treatment (Fig. 1) with robust dissociation with no sedation during treatment sessions and no changes in his pain rating (severity remained between 4-5 on the pain visual analog scale) during the course of Ketamine infusion. After 3 consecutive treatments, Mr. L reported his mood to be "markedly improved", "feeling like a fog had been lifted" and lack of suicidal thoughts and was able to carry out home chores such as yardwork and home repairs for the first time in nearly 9 months. After 4 twice per week treatments, ketamine infusions were gradually tapered down over another 4 treatments before discontinuing altogether. Patient reported doing well with sustained improvement in mood without any suicidal ideation at the time of writing this report, 4 weeks after the last

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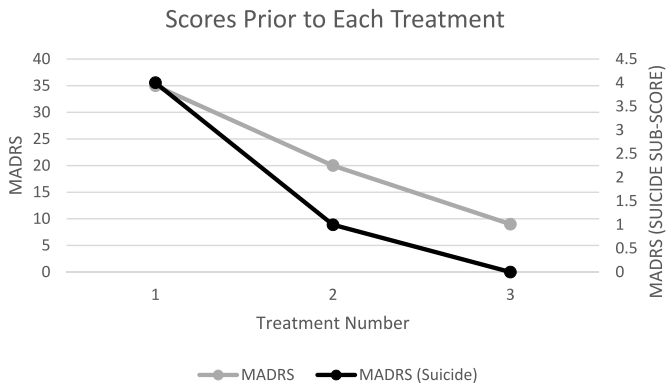

Fig. 1.

infusion.

3. Discussion

Ketamine was well tolerated and produced rapid reduction in suicidal ideations in our patient while on BPN. Additionally, the treatment had robust effects on depression. This case report provides supporting evidence that BPN does not interfere with the anti-suicidal response of Ketamine and that BPN can be safely continued in patients during IV Ketamine treatments while being maintained chronically on BPN for OUD and/or pain. Our finding is consistent with a recent report of antidepressant responses in patients maintained on BPN (Marton et al., 2019). However BPN's effects on Ketamine's antisuicidal properties are not known. We extend Marton et al's findings as we found robust and very rapid antisuicidal response (from nearly daily suicidal thoughts to none after 2 infusions) which to our knowledge has not been previously reported among patients receiving Ketamine while on BPN. While it has been suggested that naltrexone could attenuate Ketamine's antisuicidal effects (Williams et al., 2019), BPN did not interfere with rapid antisuicidal response in our patient suggesting that BPN could be continued without impacting rapid onset of Ketamine's response on suicidal thoughts.

Ketamine's underlying antidepressant/antisuicidal mechanism of action needs to be better understood as it has implications for Ketamine's use especially in vulnerable population such as those with substance use disorder (SUD) and chronic pain. It has been proposed that Ketamine may resensitize MOR after developing tolerance with long term Opioid agonist treatment (Gupta et al., 2011) and therefore Opioid receptors may have played a role in the response seen in our patient. However MOR also has an effect on pain and cardiorespiratory depression. Our patient did not experience any difference in his overall pain levels with low dose Ketamine in addition to not experiencing any toxicity which suggests BPN with its high affinity and agonist/antagonist function may have blocked Ketamine's MOR action. The net effect would be similar to Naltrexone in terms of blocking Opioid action. Others have similarly found that Naltrexone does not block Ketamine's antidepressant effects in animal models (Zhang and Hashimoto, 2019) and clinical studies (Yoon et al., 2019). A recent preclinical study found that while co-administration of Naltrexone with Ketamine blocked antidepressive-like behavioral and cellular effects in rodents, Ketamine's antidepressive effects were not due to direct MOR agonism. Instead it appears that MOR gates Ketamine's response. Therefore an intact Opioid system may be needed but not adequate for Ketamine's antidepressant response (Klein et al., 2020). Our findings suggest that in patients on partial agonist of MORs Ketamine's antisuicidal effects may be occurring through alternate pathways. Postulated mechanisms include Ketamine's antagonism of the glutamatergic NMDA receptor resulting in a glutamate surge which leads to a cascade of events that ultimately results in increased synaptic plasticity and synaptic connectivity (Abdallah et al., 2015) through Brain derived neurotrophic factor BDNF and mammalian target of rapamycin complex 1 mTORC1-dependent synapse formation (Abdallah et al., 2015; Li et al., 2010). Interestingly, a recent clinical study found that a single dose treatment with Rapamycin, an mTORC1 inhibitor, did not block but rather prolonged Ketamine's antidepressant effects (Abdallah et al., 2020).

While the debate on mechanisms of action and risk of abuse with Ketamine are ongoing due to contrasting preclinical and clinical findings, recent studies have shown that a single IV Ketamine infusion along with motivation enhancement therapy improves SUD outcomes (Dakwar et al., 2019). Patients with dual diagnoses and chronic pain have high rates of comorbid depression and suicidality. Our patient's response suggest that in controlled environments Ketamine may be a safe treatment option for rapid improvement in suicidal ideations while being on a partial MOR agonist. This is particularly pertinent with recent FDA approval of Esketamine, an S- enantiomer of Ketamine, for treatment of depressive symptoms in adults with major depressive disorder (MDD) with acute suicidal ideation or behavior ("FDA Okays New Indication for Esketamine Nasal Spray," n.d.). Our findings with a single case needs to be taken with caution and warrants further research with controlled trials on Ketamine's antisuicidal effects on those with high affinity MOR agonist to better delineate Ketamine's underlying mechanism.

Author disclosure

Avinash Hosanagar conceptualized the case report, managed the literature searches and was involved in editing of the manuscript.

Andrew Schmale wrote the first draft of the manuscript.

Andrew Leblanc was involved in editing of manuscript, data analysis, and literature review.

All authors contributed to and have approved the final manuscript.

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Declaration of Competing Interest

None of the authors have any actual or potential conflict of interest including any financial, personal or other relationships with other people or organizations within three (3) years of beginning the work submitted that could inappropriately influence, or be perceived to influence, our work.

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