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Ketamines for Treatment Resistant Depression in Patients with Chronic Pain and Opioid Use

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Abstract

Clinical use of ketamine was evaluated in 3 patients (age 36, 55, and 72 years; 2 males, one female) who suffered not only from a chronic treatment resistant depression but also from severe chronic pain for which they were prescribed opiate analgesics that they no longer wished to use due to their fear of addiction. In all 3 cases, ketamine therapy has resolved the depression, markedly decreased pre-existing high anxiety, reduced the pain to more tolerable levels, and helped these patients to avoid opiates. One of these 3 patients was afflicted with partial paralysis of his left limbs by a stroke about 2 years prior to onset of ketamine therapy: he complained of muscular tension and stiffness in these limbs, especially in his left arm and left hand, with inability to use fingers of his left hand. His muscular difficulties are reduced when on ketamine. It is of much medical interest to extend ketamine studies to patients with cerebral palsy, particularly those who suffer from chronic depression.

Keywords: *ketamine, chronic pain, opiates, treatment resistant depression, anxiety, cerebral palsy*

Introduction

Already a few years ago, both case reports and small randomized controlled trials suggested that single or repeated intravenous infusions (0.2-0.4 mg/kg) or intranasal administrations (28-84 mg) of ketamines have antidepressant action in patients with medication-refractory depression, see Andrade [1]. In much higher doses, ketamine has a high potential for abuse as a "recreational drug" with sedative and dissociative effects.

The novel medical pharmacological application of low dose ketamines is of major importance in case of severely suicidal patients resistant to usual antidepressants. The intranasal administration of ketamine seems particularly important because of its rapid action. For example, an article in *JAMA Psychiatry* by Daly, Singh, Fedgchin, et al. [2], published in 2018, reported on a double-blind trial of 67 adults with treatment-resistant depression who exhibited a significant improvement after 1 week with intranasal esketamine, 28 to 84mg administered twice weekly and the improvement appeared to be sustained with reduced dosing frequency for up to 9 weeks.

A multicenter study (Czech Republic, Germany, Poland, Spain, and USA) on 227 patients with treatment refractory depression indicated that adding esketamine nasal spray to oral antidepressants improved symptoms at 28 days, see 2019 publication by Popova, Daly, Trivedi, et al. [3].

Authors from FDA (Kim, Farchione, Potter, et al, [4]) very recently concluded that "the benefit–risk balance for this drug is favorable, and the drug represents an important addition to the treatment options for patients with treatment-resistant depression."

Since ketamine is a standard anesthetic drug, of special interest are depressed patients with a concurrent history of chronic pain. Bigman, Kunaparaju, and Bobrin [5] reported on a suicidal patient with chronic pain and concurrent use of cannabinoids. Administration of ketamine resulted in a decrease of pain to tolerable levels (without the need of alternative pain management) and a dramatic improvement in the patient's mood with resolution of his suicidality.

The present study extends the application of ketamine to patients with history of not only chronic

pain combined with a severe treatment refractory depression, but also with a history of opioid use for the pain.

Case Studies

Case Study 1

The patient is a 55 year old lady who suffered from severe depression since age 14 or 15. The depression had been associated with suicidal ideation (especially in first decades of her adult life), but so far without a suicide attempt. She had also experienced high anxiety and irritability. Since her young adult years, this patient has suffered from fibromyalgia. She was involved in 2 motor vehicle accidents (MVAs) about 20 years ago. In her first MVA, she was a pedestrian hit by a car. The impact propelled her onto the ground and she sustained a cerebral concussion. Her post-concussion syndrome included dizziness that persisted for 3 months. In her second MVA, she was involved in a collision as a car driver, sustained injures to her lumbar spine at L3 to L5, and has continued experiencing severe pain in her lower back since that time.She was also diagnosed with rheumatoid arthritis and osteoarthritis. At one time, she was on 800mg of oxycodone per day, prescribed to her by a local pain clinic.

This patient was tried on almost all major antidepressants. Their side effects included major weight gain. Her antidepressant medications at the onset of ketamine treatment were Trintillex, Cymbalta, Rexulti. Her antianxiety medication was Ativan and her analgesic medications had included codeine, Tylenol 4, Nucynta (i.e., opioid analgesics), and also anesthetic injections, every 3 months, of Marcaine with steroids into her lower back.

She was started on ketamine approximately 2 months ago, initially on 75mg every 3rd day. Given a positive response, the frequency was then increased after one month to 75mg every 2nd day. Beside the excellent antidepressant effect, this patient emphasizes the benefit of "an improved clarity of thinking, being more aware of her environment, noticing and understanding more details." The ketamine has also exerted an anti-anxiety effect and has also noticeably reduced her irritability. In contrast, she describes its analgesic effect as only "mild or minor," but still allowing her to avoid opiates.

Using the scale from 0 (no depression) to 10 (extreme depression with suicidal behavior), the patient rated her pre-ketamine depression as 9 points, and her present level of depression, since she was started on ketamine, at 2 to 3 points. Prior to ketamine, she cried every day, slept 14 to 18 hours per day, and usually felt unable to engage in her favorite hobbies such as reading.

Case Study 2

A 36 year old gentleman reported severe depression since his teens for which antidepressant medications were not helpful and resulted in adverse side-effects. His psychiatric symptoms included "racing thoughts of very depressive nature," very high level of anxiety. His most recent antidepressive medication was Wellbutrin.

He was involved in a major motor vehicle accident (MVA) about 15 years ago which resulted in a brain injury, concentration and speech problems, panic attacks, and severe pain for which he was prescribed opiate based medication. Over subsequent years, he had realized he was unable to stop using opiates.

Pharmacotherapy with ketamine resulted, within about 5 weeks, in reduced levels of depression and anxiety, an improved concentration, improved sleep, and in a decrease of speech problems.

Case Study 3

A 72 year old gentleman reported experiencing depression since his childhood and has experienced a mild lumbar pain already since his young adult years. He was raised by an alcoholic father and he himself started resorting to alcohol in the first decades of his adult life to control his anxiety and depression, but stopped about 20 years ago. During his frequent episodes of severe depression, he was apathetic, completely inactive, was refusing to go out and to talk to persons around him. Antidepressant medications had almost no effect, for example, Effexor prescribed to him about 10 years ago.

About 4 years ago, while performing repairs on a building, he fell from its roof about 5 ½ meters down onto the ground, fractured numerous bones in his feet and in his left ankle, and underwent repeated corrective surgeries during which metal screws were inserted, but had to be subsequently taken out due to infections. He disliked the effects of his prescribed analgesic opiates such as oxycodone because they "make him drowsy" and he also feared to become addicted.

Two years ago, this gentleman experienced a stroke then left him without an adequate control over his left leg and with very impaired control over his left arm and left hand. Without ketamine, the muscles in the left limbs are excessively tense, these limbs feel very stiff, and he has poor control over them. He is unable to walk properly. His left arm is held in a bent position similar to some patients with cerebral palsy and he is unable to straighten up his arm.

The treatment of this patient was at first initiated with CBD oil to help to control his pain and anxiety which has been helping somewhat, but he still experienced some residual pain and some anxiety. The subsequent ketamine treatment resulted in a remarkable decrease of depression and anxiety, in a further reduction of his chronic pain, and in an unexpected improvement of his ability to control his left limbs: his muscles are more relaxed and he is now able to even move and use fingers of his left hand over which he had no control since his stroke about 2 years ago. This suggests that low dose ketamine therapy might perhaps also be uniquely suited and beneficial for depressed adults with cerebral palsy: research in that area is much needed.

This gentleman described psychological effects of ketamine as "making him calm," emotionally relaxed, and less irritable. In his own particular case, he said that he avoids driving over the first about one to two hours after ingesting the ketamine because he feels "too relaxed" to drive, even though he feels "more mentally focused." He mentioned that the use of ketamine does not interfere with his continued use of CBD oil for pain reduction.

Discussion

Beyond the benefits of effectively addressing the treatment resistant depression in chronic pain patients, the ketamine therapy may be also particularly valuable for those of them who wish to avoid dependency on prescribed opiates, so common in the current epidemic of opiate addiction. The positive effects of ketamine reported by our patients also include a major reduction of anxiety.

An unexpected effect was observed in the elderly patient with unilateral paralysis since a stroke about 2 years ago. Without ketamine, his muscles of the left limbs are so tense and stiff that he, for example, is unable to walk properly, and has no use and control over fingers of his left hand. Ketamine helps to restore some control and use of these fingers and improve his use of left leg while walking. The ketamine provides him with a major reduction of the excessive muscular tension and stiffness while improving the overall muscle control: it would be of much medical interest to extend the ketamine studies to patients with cerebral palsy who suffer from chronic depression.

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