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Effect of a single dose of intravenous ketamine on the wish to hasten death in palliative care: A case report in advanced cancer

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Case Report

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Abstract

Objectives. The suffering experienced by some patients at the end of their lives can lead to a wish to hasten death (WTHD). It is sometimes an existential suffering, refractory to palliative care even if well conducted, which leads to this desire. Since several years, in psychiatry, the rapid anti-suicidal effects of a single injection of ketamine have been proven. WTHD and suicidal ideation have similarities. The injection of a single dose of ketamine could have an efficiency on the desire to hasten death.

Methods. We report the case of a woman with advanced breast cancer expressing a WTHD, treated by ketamine.

Results. A 78-year-old woman expressed a WTHD (request for euthanasia) because of existential suffering following a loss of autonomy related to cancer. The suicide item was 4 on the Montgomery–Åsberg Depression Rating Scale (MADRS). She had no associated pain or depression. A single dose of intravenous ketamine 1 mg/kg over 40 min plus 1 mg of midazolam was injected. She had no adverse effects. From D1 post-injection to D3, the WTHD disappeared completely with a MADRS suicide item at 0. At D5, the WTHD started to reappear, and at D6, the previous speech was completely back.

Significance of the results. These results suggest an effect of ketamine on WTHD. This opens up the possibility of treating existential suffering at the end of life. The optimal dosage of this treatment would have to be determined as well as a maintenance of efficacy scheme.

Introduction

Some people with severe and incurable illnesses in advanced stages of disease express a desire to hasten their death. This is referred to as a "wish to hasten death" (WTHD) (Balaguer et al. 2016), distinguished from acceptance of the occurrence of death. This desire is a reaction to suffering for which hastened death seems to be the only way out. When this suffering is relieved, or diminished enough to be tolerable, the desire to hasten death often disappears. This situation is well known in palliative care (Guirimand et al. 2014).

Some of these requests are the result of what is called existential suffering (Greer et al. 2018). This suffering, sometimes associated with no other symptoms, is refractory to drug treatments or multidisciplinary care and support. A consequence of this desire may be an explicit request to hasten death and may lead to euthanasia, assisted suicide, or sedation, depending on the country's legislation.

Suicidal ideation, often referred to as suicidal thoughts or ideas, is an umbrella term used to describe a range of contemplations, wishes, and concerns about death and suicide . Thus defined, WTHD and suicidal crisis may have proximity.

The psychotropic properties of ketamine have been studied since the 1960s (Krystal et al. 2019; Mathai et al. 2022; Walsh et al. 2022). This molecule has been shown to be medically effective in treating depression, particularly refractory depression, and suicidal crisis. These 2 effects seem to be independent of each other. The treatment consists of a single injection of ketamine 0.5 mg/kg intravenously over 40 min in most cases (Wilkinson et al. 2018), sometimes up to 3 mg/kg (Reinstatler and Youssef 2015). Efficacy is observed in less than 24 h and lasts for approximately 2 weeks for the antidepressant effect and 3–5 days for the anti-suicidal effect (Wilkinson et al. 2018).

Its rapid action makes this use of ketamine particularly attractive in palliative care when the life span is limited. The antidepressant effect has been illustrated by several case series in palliative care that showed delayed efficacy when given orally daily (Irwin et al. 2013), or more recently with a subcutaneous injection of ketamine followed by an oral maintenance dose

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(Latuga et al. 2021). The anti-suicidal effect was illustrated by a case in which a single intravenous (IV) injection of ketamine (0.5 mg/kg) combined with sertraline (50 mg/day) resulted in the rapid disappearance of a suicidal risk in late-stage cancers (Rodríguez-Mayoral et al. 2020). While these case reports are of limited scientific evidence, they highlight the potential value of psychotropic ketamine in palliative care, particularly for suicidal ideation.

We report here a case suggesting that the anti-suicidal effect of ketamine may have an effect on this existentially driven WTHD.

Case report

The patient is a 78-year-old woman with advanced multimetastatic breast cancer, in exclusive palliative care, with no evidence of brain metastases. For the past 5 years, following an infectious episode unrelated to the cancer, she has had a major motor disability of the lower limbs for which she has undergone rehabilitation and regained satisfactory autonomy.

Her condition has deteriorated over the last few months and she has lost her autonomy due to cancer-related asthenia. At the time the mobile palliative care team met her, she was hospitalized in a conventional oncology ward. The team had been called because she was repeatedly asking the nursing staff on a daily basis to die and to be euthanized. The loss of autonomy and the absence of hope for improvement made her life meaningless and provoked this desire to die. She was suffering from an existential origin.

In France, euthanasia is illegal. She knew this but continued to express the desire to die.

She was not in pain and had no painkillers. Unfortunately, for practical reasons, she did not see a psychiatrist or psychologist. She had mild anxiety on the Hamilton scale with a score of 10, and mild depression on the Montgomery–Åsberg Depression Rating Scale (MADRS) with a score of 24. In response to her WTHD, alprazolam had been prescribed 10 days earlier and citalopram 20 mg 7 days earlier with no effect on her desire. She was bedridden with a Karnofsky index of 40%. Her life expectancy was not predicted in the short term.

Her desire to hasten death was assessed on the MADRS suicide item 10 with a score of 4 "Probably better off dead. Suicidal thoughts are common, and suicide is considered as a possible solution, but without a specific plan or intention."

She agreed to try an unconventional treatment and received a single injection of ketamine 1 mg/kg over 40 min, with 1 mg of midazolam at the beginning of the injection to limit the risk of psychodysleptic syndrome. No other changes in her treatment were made. No adverse effects were observed.

At D1 post-injection, she no longer had a desire to die. The MADRS suicide item in hetero-assessment was 0: "Enjoys life or takes it as it comes."

She felt ashamed of her death wishes. Several changes were observed in her speech. She viewed some family projects positively: they seemed to open up the future for her, whereas before they only reinforced her lack of hope. She also viewed positively some of the concerns of her relatives that she had previously spoken of in a very pejorative way. She had reminiscences of memories, but positive ones.

At D4, her speech became more dark. At D5, she again expressed a desire to die, and at D6, her previous speech had completely returned.

At D8, she was transferred to another facility where she developed a lung infection. Her condition deteriorated quite suddenly and she died a week later.

Discussion

In this case, an effect of ketamine was observed by transiently suppressing a desire to hasten death of existential origin. The duration of its efficacy, between 3 and 5 days, is in agreement with the duration of the anti-suicidal effect found in the literature. The confounding factor could have been the antidepressant effect of ketamine. However, the patient was only slightly depressed, and the expected antidepressant effect of ketamine would have been longer. The return to the previous state at D6 shows that the observed effect is not related to the introduction of citalopram at D7.

It should be noted that the 1-mg/kg dose is higher than that typically used in psychiatric studies even though doses of 1 mg/kg have been used (Wan et al. 2015). The effective dosage against WTHD should be clarified.

The main limitation of the observed effect is its brevity. To be relevant in daily practice, a maintenance dose should be considered. Several protocols are being studied to prolong the antidepressant effect of ketamine. It would be possible to draw inspiration from them for the anti-suicidal effect against WTHD: a maintenance dose by IV ketamine injection 3 times a week as tested (Phillips et al. 2020) and then once a week. Because the IV form may not be suitable for home palliative care or certain situations, a daily oral dose of 1 mg/kg ketamine (Irwin et al. 2013) or subcutaneous injection may be alternatives.

The mechanism of action of ketamine in this situation is uncertain. In mental health, ketamine can be used in 2 different paradigms: the pharmacological paradigm (as an antidepressant and anti-suicidal agent) and the psychedelic-assisted therapy paradigm/enhanced psychotherapy (where ketamine's effects, including its acute subjective effects, are integrated with psychological interventions) (Muscat et al. 2021). Considering that there is currently emerging research on the use of psychedelic-assisted therapy for death anxiety related to cancer and for palliative care (Kolp et al. 2007; Rosenbaum et al. 2019; Ross 2018), it is possible that it was the psychedelic effect of ketamine that was effective in this clinical case.

In this hypothesis, assisting the injection of ketamine with psychotherapy could potentiate its effectiveness in intensity and duration. The injection of midazolam to prevent the psychodysleptic effect could have the undesirable effect of limiting the efficacy of ketamine, as is already known, and should therefore be avoided.

In any case, ketamine opens a door to the relief of existential suffering in the desire to hasten death. If confirmed by dedicated prospective studies, this drug treatment should be considered as part of a global management, in the same way that analgesics are essential to relieve pain but cannot be used without a multimodal treatment.

Finally, the potential effectiveness of ketamine on existential suffering also raises ethical and philosophical questions:

- Ethics: Is it legitimate to consider existential suffering as refractory without attempting this type of treatment and to practice definitive acts such as sedation, assisted suicide, and euthanasia?
- Anthropological: In case of effectiveness linked only to the pharmacological paradigm, how can a drug treatment act on the existential, even spiritual part of a person, often considered as the most intimate of the being?
- Epistemological: Is it the place of medicine to act on this intimate component of the being, considered by some as the ultimate space of freedom?

Conflicts of interest. No competing financial interests exist for any author.

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