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Case Report

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# When Midazolam Fails and the Professional Twitches: Propofol for Palliative Sedation

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## Abstract

Delirium with refractory agitation is a common indication for palliative sedation. Significant distress and suffering can be experienced by patients, relatives and caregivers when conventional palliative sedation strategies fail in end-of-life situations. We present a case report of a cancer patient where the use of propofol in the treatment of hyperactive delirium with agitation refractory to palliative sedation with midazolam was rapidly effective, illustrating the relevance of managing the suffering created by this challenging clinical scenario in the palliative care setting. Despite the fact that suboptimal results in palliative sedation are not infrequent, medications such as propofol are rarely used. Thus, the case exposed aims at helping other healthcare professionals handle the difficult situation that arises when conventional sedation fails, generating much suffering in all the parties involved, by proposing the use and titration of propofol by skilled professionals.

**Keywords:** Delirium; Palliative Sedation; Propofol; Suffering

## Introduction

A variable proportion of cancer patients will require sedation at the end of life. Palliative sedation is defined as the deliberate lowering of consciousness to alleviate severe suffering from refractory symptoms [1]. If conventional palliative sedation strategies are not effective, the suffering worsens for the patient, his family and the healthcare team involved. Therefore, it is crucial for medical professionals that are in frequent contact with patients at the end of life to have varied and effective tools for approaching these situations.

## Case Description

We present the case of a 65-year-old man with diagnosis of metastatic lung adenocarcinoma with adrenal, bone and brain involvement, who had received systemic chemotherapy treatment according to the standard regimen and radiotherapy on the two known brain lesions. He was admitted for severe delirium consisting of disorientation to time and place environment, impaired attention, language disturbance with incoherent speech and predominantly nocturnal agitation. As past medical history the patient had a depressive disorder with a recent attempt of suicide, moderate cognitive impairment and a history of alcohol use disorder. Upon physical examination he lacked orientation in time, was not responsive to verbal commands and had communication impairment, without other relevant findings. No significant alterations were evidenced in the blood tests performed. A brain magnetic resonance was indicated showing an increase in size of one of the already known lesions located in the right occipital region with increased mass effect.

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Treatment with dexamethasone 4 mg Q6H after an initial bolus of 10 mg was started to diminish cerebral edema. For agitation control, quetiapine 25 mg/day and levomepromazine 12.5 mg as rescue medication were initiated, with poor clinical response and few changes in delirium symptoms mentioned and agitation [Richmond Agitation-Sedation Scale (RASS) score: +3]. For this reason, glucocorticoid titration was reduced to 8 mg/day to avoid worsening agitation and neuroleptic treatment was adjusted with quetiapine 50 mg/day and 5 mg midazolam boluses as rescue medication. This medication was able to control restlessness during the day but not at night. After deliberating with the involved teams and the patient's family, palliative sedation for refractory agitation was started. Neuroleptic treatment with quetiapine was withdrawn and continuous intravenous infusion of midazolam at 2 mg/h was started with two initial boluses of 5 mg to induce sedation. As adjuvant treatment, levomepromazine boluses were used with a requirement of 75 mg in the first 4 hours. Despite the medication administered and progressive dose increase in midazolam infusion, agitation and aggressiveness persisted with risk of injury to the self and others (RASS score: +4).

Four hours after palliative sedation initiation, the oncology resident attending the patient assessed the situation identifying unbearable suffering in the patient, his relatives and the nursing team at care for the patient. She consulted the palliative care specialist to evaluate the patient and both decided, after family communication and consent, to activate the protocol for refractory sedation. Glucocorticoid treatment was withdrawn and palliative sedation with intravenous propofol was initiated administering a 10 mg bolus and starting a continuous infusion with a 50 mL ampoule of propofol lipide 1% at 100 mg/h. In a few minutes, deep sedation was induced whilst maintaining a good respiratory pattern (RASS score: -4). Twelve hours after starting propofol infusion, during the medical visit, the patient was stimulated to check the level of sedation. He woke up briefly and sympathetically expressed the satisfaction with the rest experienced (RASS score: -2). Throughout the day, propofol infusion was adjusted to 150 mg/h to maintain an appropriate level of sedation. The patient died very calm 24 hours after starting propofol treatment. The relatives expressed their gratitude to the medical team. The professionals attending the patient were satisfied with the decision-making process and the effectiveness of the treatment as it fulfilled the goal of pacifying the situation and, therefore, diminishing the distress experienced in all parties involved. The young oncology resident and the palliative care specialist made the decision to communicate the case for it could serve others as a learning experience to handle difficult situations with coexisting patient's, relatives' and health professionals' suffering.

## Discussion

Delirium has been reported in 13 – 42% of patients admitted to palliative services and above 80% of patients in the period prior to death [2-4]. Delirium is a common clinical syndrome resulting from global organic cerebral dysfunction that entails impaired attention, awareness and cognition [2,5]. Incidence rates increase in cancer patients and represents an independent factor for morbidity and mortality for this subset population [6]. Some delirium predisposing factors such as age, brain metastases and antineoplastic treatments have been characterized in cancer patients [4]. Delirium with refractory agitation is the most frequent indication for palliative sedation [7-9]. The case report describes a patients with advanced non-small cell lung cancer and delirium predisposing comorbidities such as brain radiotherapy for central nervous system (SNC) metastases, pre-existing cognitive impairment and previous alcohol use disorder that presented refractory delirium with agitation for which palliative sedation was indicated.

Once delirium is diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5) diagnostic criteria [10], communication with the family and an adequate management approach is crucial since evidence suggests that approximately 50% of delirium episodes in palliative care setting can be reversed [4,11]. It is essential for delirium treatment to be interdisciplinary, coordinating non-pharmacological interventions and a pharmacological treatment. Non-pharmacological procedures include the management of reversible precipitating factors, optimization of sleep-wake pattern, cessation of unnecessary psychoactive medication, a bladder and bowel care and the monitoring of hydration and nutrition [4,11]. Since a neurotransmitter dysregulation is thought to underlie the pathophysiology of delirium, treatment with antipsychotics of first, second and third generation have been widely used in clinical practice, although evidence available from randomized controlled trials is scarce [2]. In the presented case report, diagnosis of delirium was suspected at admission in a cancer patient with previously treated brain metastases. For this reason, CNS imaging was performed evidencing size increase in right occipital known lesion in probable relation to radiotherapy-induced changes. Although corticosteroids might have a neuropsychiatric effect worsening some delirium symptoms and agitation [4], dexamethasone was prescribed to reduce cerebral edema and antipsychotic treatment added for delirium management.

Delirium causes significant distress to both patients and caregivers [6]. It can potentially deteriorate their quality of life and have a negative effect in patient's morbidity and mortality [13,14]. Delirium can affect patients, families, and health providers in complex and distressing ways, producing a physical and psychological burden [15]. Patients with delirium often feel helpless, abandoned and rejected by family caregivers and healthcare professionals [16]. As they can feel threatened, they might show a tendency to aggressiveness, refusing to receive medical attention and trying to escape from

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the terrifying situation they experience during the confusional state [17]. Patient burden can be related with the memory of lived experiences such as fear and hallucinations, the potential awareness that at that time they were not capable to distinguish between the real and the unreal, and the imaginary immersion in scenes with a large emotional component [16]. The unexpected, rapid and unpredictable nature of delirium can be particularly distressing on the patient's family. The main elements determining family burden are the uncertainty about current situation, the possible need for additional support, the fear of the impact on their health, the limitation of social activity and the emotional exaltation. Lack of awareness of the disorder heightens the difficulty of understanding the sudden changes in behavior and emotions of the relative they are caring for and contribute to appearance of feelings of distress for caregivers [18]. Anxiety, frustration, depression and stress are emotional states that are frequently reported by relatives of patients with delirium [6]. Health care personnel burden has been attributed to the unpredictable course of delirium, fear for their own safety, uncertainty about how to meet patients' needs, increased workload, and frustration due to the lack of knowledge about the best strategy to follow [17]. This emotional toll has demonstrated to be higher when caring for patients with hyperactive delirium [19]. In the case described, the patient presented delirium with agitation that was refractory to both neuroleptic treatment and conventional palliative sedation. Patient's family and the health team caring for the patient experienced high levels of frustration and distress, evidencing how the suffering that they were intending to relive became unbearable.

Midazolam is the most frequent treatment used for palliative sedation, predominantly as a single agent by intravenous or subcutaneous continuous infusion [8,9,20,21]. Although health providers have reported suboptimal results in the efficacy of palliative sedation in up to 50% of cases [9,22,23], less than 10% of patients with palliative sedation receive medication for refractory episodes with alternative options such as propofol or phenobarbital [8,9,20,21]. The most widely used palliative sedation clinical practice guidelines [1,4,24] and the European Association for Palliative Care (EAPC) recommended framework for palliative sedation [25] propose the use of propofol, in a hospital setting and under supervision, as an alternative treatment for refractory situations such as the case described, in which it was indicated and administered by the palliative care specialists.

Propofol is an anesthetic drug that causes central nervous system depression by potentiating gamma-aminoburitic acid a receptors ($GABA_A$) and possibly by glutamate inhibition [26]. Its advantages in palliative sedation include a quick onset of sedation (its onset of action is in 30 seconds and reaches its maximum effect in 90 seconds when administered in intravenous bolus and 20-30 minutes when administered in continuous infusion [27,28]), the ability to rapidly titrate and a rapid washout [24,28,29]. Propofol has a large inter-individual variation regardless of dose and plasma concentration [30]. The recommended dosage is a 20 – 50 mg iv bolus, followed by continuous infusion at 20 mg/h, increasing by 10 mg/h every 15 minutes until the optimal level of sedation is reached [24]. Otherwise, reported cases and retrospective studies describe initial infusions at 1 mg/kg/h, progressively titrating up to maximum doses of 4 mg/kg/h [28].

Although the dosage used for palliative sedation is much lower than the one used in anesthesia, prescribers and nurses who care for patients with propofol palliative sedation must be aware of its pharmacokinetics and pharmacodynamics in order for it to be administered safely and effectively. Propofol administration requires capable and experienced facultatives, as it may require frequent adjustments, it has a very fast onset of action and recovery, and has a potential risk of side effects such as hypotension and respiratory depression [29]. Potential side effects appear more frequently in elderly patients [28,30,31], when given at high doses and rapid infusions [28,30,31]. In the case described, initial 10 mg bolus was administered achieving a rapid suitable level of sedation with a good respiratory pattern and continuous infusion was maintained at 1.2 mg/kg/h with progressive subsequent increase until 1.5 mg/kg/h.

In our center, we have a protocol for propofol use in refractory palliative sedation approved by the Pharmacology and the Anesthesia Departments. The most significant result observed since the protocol development is that the use of propofol in the indicated cases relieves situations of high suffering as the one previously described. It is crucial that the indication and monitoring of propofol for palliative sedation is performed by an experienced professional. International guideline criteria establish that in centers where there is no established protocol for the use of propofol in refractory sedation, an anesthesiologist should be consulted [24].

## Conclusions

A proportion of patients with palliative sedation are refractory to conventional treatment producing highly distressing situations such as the one illustrated above. Severe suffering around a patient at the end of life can be successfully treated with propofol. Skilled observation and dose titration throughout the period of palliative sedation with propofol is necessary.

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## Disclosures

The authors declare no conflicts of interest.

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