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Clinical and ethical aspects of palliative sedation with propofol—A retrospective quantitative and qualitative study

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Background: The anesthetic propofol is often mentioned as a drug that can be used in palliative sedation. The existing literature of how to use propofol in palliative sedation is scarce, with lack of information about how propofol could be initiated for palliative sedation, doses and treatment outcomes.

Aim: To describe the patient population, previous and concomitant medication, and clinical outcome when propofol was used for palliative sedation.

Methods: A retrospective study with quantitative and qualitative data. All patients who during a 4.5-year period received propofol for palliative sedation at the Department of palliative medicine, Akershus University Hospital, Norway were included.

Results: Fourteen patients were included. In six patients the main indication for palliative sedation was pain, in seven dyspnoea and in one delirium. In eight of these cases propofol was chosen because of the pharmacokinetic properties (rapid effect), and in the remaining cases propofol was chosen because midazolam in spite of dose titration failed to provide sufficient symptom relief. In all patients sedation and adequate symptom control was achieved during manual dose titration. During the maintenance phase three of 14 patients had spontaneous awakenings. At death, propofol doses ranged from 60 to 340 mg/hour.

Conclusions: Severe suffering at the end of life can be successfully treated with propofol for palliative sedation. This can be performed in palliative medicine wards, but skilled observation and dose titration throughout the period of palliative sedation is necessary. Successful initial sedation does not guarantee uninterrupted sedation until death.

Editorial Comment: In palliative care, some patients at the end of life can reach a stage where there have been maximal analgesic and or anxiolytic treatments though without achieving comfort in the awake state. This report describes and discusses use of propofol in these infrequent cases to relieve suffering as part of palliative care.

1 | INTRODUCTION

Palliative sedation is a treatment option if pain, dyspnoea, delirium, or other symptoms in a terminal patient cannot be relieved in an awake state.[1-3] The essence of palliative sedation is that infusions of analgesics and sedatives are titrated until the patient is sufficiently sedated to not experience suffering.

The anesthetic propofol is often mentioned as a drug that can be used in palliative sedation if benzodiazepines do not provide sufficient symptom relief or sedation.[3-6] Propofol is a potent anesthetic with sedative but not analgesic properties. It is acts rapidy and thus is suitable for rapid dose titration.[7] Even though the first case reports of use of propofol in palliative sedation were published more than 20 years ago[8,9] the existing literature of how to use propofol in palliative sedation is scarce,[3,10] with lack of information about how propofol could be initiated for palliative sedation, doses, and treatment outcomes. The largest case series of use of propofol in palliative medicine was published in 2005,[11] but did not specifically address the use of propofol in palliative sedation. In a recent comprehensive review on the use of propofol for palliative sedation the vast majority of data and recommendations were based on inference from other patient populations and indications.[12]

Palliative sedation presupposes awareness, knowledge, and skills in the recognition of palliative care needs and interventions.[13] The initiation of palliative sedation furthermore requires communication with patients and next of kin about treatment goals and options as part of shared decision-making.[14,15] Research is lacking on how physicians document the patients' symptom burden and the decision process before the decision to start palliative sedation is reached.

The present study is an evaluation of all cases where propofol was used for palliative sedation at the Department of Palliative Medicine, Akershus University Hospital (Ahus) during a 4-year period. The aim was to describe the patient population regarding demographic data, disease, symptom burden, previous and concomitant medication, and clinical outcome when propofol was used for palliative sedation. Furthermore, doctors' notes in patient records were examined for cues regarding awareness of suffering, involvement of patients and families in decision-making, and potential barriers to adequate symptom relief.

2 | MATERIALS AND METHODS

2.1 | Study design, population, and setting

This is a retrospective study. All patients who during the period between April 1st 2014 and September 1st 2018 received propofol for palliative sedation at the Department of palliative medicine, Ahus, Lørenskog, Norway, were included. Ahus is a public hospital which serves an unselected population of approximately 500 000 people. The department of palliative medicine has nine beds for inpatients. Senior consultants in palliative medicine are on call around the clock. Patients were identified based on the treating physicians' knowledge of the patients who had received palliative sedation with propofol.

2.2 | Propofol treatment

There was no formal protocol for administration of propofol for palliative sedation, but consensus among the senior consultants regarding how to perform this procedure. For each individual patient the decision to provide palliative sedation with propofol was made by two senior consultants after multidisciplinary evaluation. Treatment commenced with a 30- to 60-minute manual titration phase. During this phase, propofol was administered as repeated intravenous bolus doses of 10-30 mg by one of the senior consultants at the department who were trained as anesthesiologists. After this initial titration phase an intravenous infusion was started based on the dose requirement during the manual titration phase. During treatment with continuous infusion, nurses could administer bolus doses as needed. Bolus doses ranged from 10 to 40 mg, depending on infusion rate. Bolus doses could be administered with 5-minute intervals. The infusion rate and bolus doses were adjusted by senior consultants in palliative medicine. The clinical effect and the need for further increases in dose were evaluated bedside by nurses and physicians.

2.3 | Data collection and variables

All data were collected from the electronic patient files. Two of the researchers independently extracted data from the patient files. Subsequently the two sets of data were compared, and in cases of discrepancy, a joint decision was reached.

The qualitative data analysis was performed by two authors independently, by the use of a qualitative, hermeneutical technique based on a deconstruction and reconstruction of the text. The text consisted of all medical notes made by various physicians during the last week before death. The aim of these analyses was a better understanding of the phenomenon of profound suffering ultimately leading to palliative sedation.

The researchers' pre-understanding and conceptual framework was influenced by a common experience that patients' pain is often unrecognized, unrelieved, and perceived differently among patients and observers. In order to capture these different perspectives, we specified three overarching themes beforehand as follows: patient-related, physician-related, and text referring to family/next of kin. The analysis was performed independently by two authors by regrouping the text elements. All text elements with wording, content, or perceived meaning in line with the research themes were included. For each theme emerging characteristics and subthemes were identified and meaningful text and illustrating quotes were marked and described. Identification of characteristics, themes, and quotes were validated by a structured search for contradictive understanding and negative quotes. Descriptions, themes, and quotes were also validated against the original text, and additional themes not included in the pre-defined themes were searched for. The validating process also included a face validity test by all authors. The researchers were blinded to the identity of the physicians involved during the text analysis. Because some of the patients were transferred from other wards

to the palliative medicine ward less than 1 week before death, some of the text included in the text analysis has been written by physicians at other departments.

2.4 | Statistics

Descriptive statistics were used as appropriate, mainly as mean values. Some data are presented separately for the main indications, which were pain and dyspnoea. The number of patients is too small for statistical testing of differences between subgroups.

2.5 | Research ethics

The study was approved by the Regional committee for medical and health research ethics, Region South East (Application 2018/424). The project was also approved by the local Data protection officer at Akershus University Hospital.

3 | RESULTS

3.1 | Study population

Fourteen patients who had received palliative sedation with propofol were included, four females and 10 males, with a mean age of 48 years (range 14-78) Table 1. For two patients, the palliative sedation was performed at the pediatric ward and an intermediate care ward, respectively. Eight of the patients died from cancer, three from amyotrophic lateral sclerosis (ALS), and three from other causes.

3.2 | Indication for palliative sedation

In six patients, the main indication for palliative sedation was pain, in seven dyspnoea, and in one delirium. In eight of these cases propofol was chosen because of the pharmacokinetic properties (rapid effect), and in the remaining cases it was midazolam which, in spite of dose titration, failed to provide sufficient symptom relief. Eleven patients were awake and consented to the use of propofol before it was started. In the remaining three cases, the decision was based on an advance directive, joint decision with next of kin, or decision by health care personnel alone, respectively. Pausing the infusion of sedatives in order to wake the patient and re-evaluate the indication was neither planned nor performed in any of the patients.

3.3 | Life-prolonging treatment

In four patients, the palliative sedation with propofol was started because intolerable symptoms were expected due to withdrawal of life-prolonging treatment. Three patients terminated treatment with Bipap/VPAP-masks and one patient high-flow oxygen treatment (Optiflow). These life-prolonging respiratory support treatments were withdrawn when a stable sedation had been reached. In the

TABLE 1 Characteristics of patients who received propofol for palliative sedation

Main symptom	Diagnose	Age	Days spent in hospital before palliative sedation	Ability to consent	Withdrawn treatment	Time from propofol to death
Dyspnoe	ALS	70	1	Yes	None	<24 hours
Dyspnoe	ALS	72	2	Yes	Bipapmask	<24 hours
Dyspnoe	Uterine cancer	78	2	Advance directive	None	<24 hours
Dyspnoe	ALS	38	8	Yes	VPAP	<24 hours
Dyspnoe	Spastic paraplegia	30	10 Medical intensive dep. the whole period	Yes	None	<24 hours
Dyspnoe	Fibrosis of lung	78	1	Yes	Oxyflow	<24 hours
Dyspnoe	Adrenal carcinoma	51	15	Yes	None	24-48 hours
Pain	Vesical cancer	54	4	Yes	None	24-48 hours
Pain	Congenital disability, intestinal dysfunction	14	2 Pediatric dep. the whole period	Next of kin	Bipap	24-48 hours
Pain	Hepatocellular carcinoma	42	8	Yes	None	<24 hours
Pain	Neuroendocrine pancreatic ca.	57	7	Health care personell alone	None	24-48 hours
Pain	Rectosigmoidal cancer	41	13	yes	None	5 days
Pain	Pulmonal cancer	28	1	yes	None	<24 hours
Delirium	Glioblastoma	30	2	yes	None	<24 hours

remaining patients all life-prolonging treatments had been terminated at an earlier stage. None of the patients received any life-prolonging treatment including fluids/hydration after start of palliative sedation with propofol. During palliative sedation no monitoring or recording of vital signs was performed.

3.4 | Survival

Nine of the 14 patients died within 24 hours after start of propofol for palliative sedation. Four of the remaining patients died between 24 and 48 hours after start of propofol, whereas one patient died 5 days after start of propofol. Overall, survival appeared to be shorter in patients who received palliative sedation with propofol for dyspnoea than in patients with pain as indication.

3.5 | Drug doses

3.5.1 | Before palliative sedation

In all patients who received palliative sedation with propofol for pain, the opioid treatment had been titrated to doses of 10-50 mg/hour of intravenous morphine or oxycodone and supplemented with ketamine infusion Table 2. One of these patients also received a methadone infusion. With the exception of one patient who received 20 mg/hour of intravenous morphine, the patients who received palliative sedation for dyspnoea received low or moderate morphine doses of 1.3 to 6 mg/hour. With the exception of one patient, all patients had received midazolam infusion before start of propofol, with doses ranging from 0.4 to 7.5 mg/hour.

3.5.2 | At death

At death propofol doses ranged from 60 to 340 mg/hour Table 1. Opioids, ketamine, and midazolam were continued. Doses of opioids and/or ketamine had been increased in all patients who received palliative sedation with propofol due to pain.

3.6 | Clinical outcomes

In all patients, sedation and adequate symptom control was achieved during manual dose titration. During the maintenance phase, three of 14 patients had spontaneous awakenings where they were able to verbally communicate and/or change body posture from a supine to a sitting position. In all patients who had spontaneous awakenings, sedation and symptom control was re-established and maintained after use of bolus doses and further dose titration. Two of the patients who had life-prolonging treatment withdrawn after sedation had been achieved by manual titration of propofol, died before start of continuous infusion with propofol.

3.7 | Side effects and complications

One of the 14 patients had a transient respiratory depression with respiratory rate below 6/min during dose titration, with subsequent normalization of respiration without any intervention. One patient experienced airway obstruction during dose titration, but responded to jaw-thrust and had a normal respiratory rate. No patients had a circulatory collapse during dose titration.

3.8 | Qualitative analyses

3.8.1 | Patient-oriented text

The patient-oriented text was divided into two subthemes, with the following characteristics.

3.8.2 | Severe suffering

Descriptions of intense suffering were frequent and present in all patients included in the study. Perception of pain was based on verbal and non-verbal expression.

> "NN has the whole time been in great pain, without sufficient relief by high doses of opioids. He has expressed anxiety that he will not receive adequate pain relief medication when sleeping, with no capacity of expressing himself"
>
> 28 year-old-male patient with extensive cancer disease

3.8.3 | End of life care preferences

The references to patients' death wishes were direct and frequent:

> "The patient clearly states that she feels very ill and that she wants to die."
>
> 70-year-old female patient with advanced ALS

Furthermore, these statements were repeated on several occasions and by various physicians:

> "She clearly states that she does not want to be put on a respirator, and that she does not want ventilation support. She repeats again that she wants us to terminate the ventilation support therapy"
>
> 70-year-old female patient with advanced ALS

TABLE 2 Indication for using propofol, and drug doses of analgesics. and sedatives before start of propofol and at death

Indication for propofol	Doses before propofol (mg/hour infusion)					Doses at death (mg/hour infusion)					
	Morphine	Oxycodone	Ketamine	Methadone	Midazolam	Propofol	Morphine	Oxycodone	Ketamine	Methadone	Midazolam
Pharmacokinetics	1.3				1.7	20.0	2.0				1.7
Midazolame failed	1.3				0.8	60.0	1.3				0.8
Pharmacokinetics	3.0				4.2	[a]	3.0				4.2
Midazolame failed	1.5				4.2	70.0	1.5				4.2
Pharmacokinetics	[a]										
Midazolame failed	16.0		20.0	4.2	3.5	160.0			40.0	4.2	4.2
Midazolame failed			10.0		7.5	60.0			15.0		7.5
Midazolame failed	40.0		8.4		2.5	200.0	72.0		8.4		2.5
Pharmacokinetics						65.0	1.7				2.0
Midazolame failed		48.0	2.1		1.7	200.0		48.0	4.2		1.7
Pharmacokinetics	10.0		4.2		0.2	340.0	10.0		8.4		2.5
Pharmacokinetics	6.0				1.2	[a]	6.0				1.2
Pharmacokinetics	20.0				0.4	240.0	20.0				2.1
Pharmacokinetics	36.0		3.1		2.1	100.0	36.0		5.2		2.1

[a]Patient died before start of continuous infusion.

One striking observation was the frequent lack of acknowledgment in the patient charts of the doctor's response, strategies, or measures to reduce the symptoms in question or honor the patients' wishes. Often description of pain and distress were followed by paragraphs on medical data not connected to patients' experiences at all.

3.8.4 | Physician-oriented text

The physician-oriented text was divided into three subthemes:

8.4.1 | Medical data

Medical findings and planned tests and procedures constituted by far the largest part of the medical notes. However, occasionally did these data include a focus on the palliative situation, symptom relief, and the expressed wishes of the patient, as illustrated by the following quote:

> "Due to increasing respiration problems and anxiety, we have decided to add sedative treatment with…."
>
> 28-year-old male patient with lung cancer

8.4.2 | Reflection on the situation and palliative treatment plan

Both themes became more frequent close to the palliative sedation decision:

> "It is her right to decide on terminating further treatment"
>
> "After discussion in the team we have decided to offer her palliative sedation in order to terminate ventilation support without any symptoms and suffering on her part"
>
> 72-year old

In one patient only measures contrary to the patient's expressed wishes (to terminate all life-prolonging therapy) were decided:

> "We will continue physiotherapy, and measures for mucous mobilisation that he does not want, be we should continuously offer it to him"
>
> 30-year-old male patient with respiratory failure due to spastic paraplegia

8.4.3 | Text addressing relatives/next of kin

The text mentioning relatives or next of kin was surprisingly meagre, and was characterized by descriptions of their presence, statements confirming the level of suffering, and the expression of support, understanding, and gratefulness as illuminated by the following quotes:

> "His mother has been with him continuously the last week"
>
> 32-year-old male patient with glioblastoma
>
> "The sons say that he has suffered a lot lately and he has repeatedly said he wants to die."
>
> 78-year-old male patient with advanced interstitial pulmonary disease.
>
> "The family is grateful that his suffering is ending"
>
> 54-year-old male patient with metastatic bladder cancer.

4 | DISCUSSION

This study confirms that propofol can successfully be used in palliative sedation, and adds novel and detailed information on drug doses, dose titration, and treatment outcomes. Another important message is that extensive suffering had been documented by physicians during several days before palliative sedation was initiated.

4.1 | Barriers and delays

The qualitative analysis indicates a time lag in the process leading up to palliative sedation. During this time lag patients were supported very much by family members and were ahead of the physicians in their recognition of insufficient symptom relief. Physicians are likely to be influenced by their tradition's emphasis on additional diagnostic tests and procedures, an approach which is more meaningful in potential curative conditions. Even though the palliative approach at the end of life strongly emphasizes pain relief, the present study indicates that even at a palliative ward there might be delays in instigating necessary measures to relieve suffering.[16]

Physicians have often been criticized for a lack of awareness of patients' suffering. This was not supported by findings in the present study where suffering was documented in patient charts. However, the physicians' awareness was documented largely by repeating the patients' own expressions. Furthermore, it is an important finding the awareness of suffering did not immediately lead to instigation of sufficient measures. This delay may have been caused by a lack of knowledge of advanced pain treatment options, a well-known physician barrier to optimal pain control.[17] It can be speculated that even experienced consultants in palliative medicine have barriers toward the initiation of palliative

sedation with propofol. One such barrier might be national guidelines stating that "all other measures must have been attempted" before palliative sedation is initiated.[18] This can cause physicians to employ other treatment strategies, even in cases where they might consider palliative sedation with propofol the best treatment option.

4.2 | Clinical issues

The included patients were given propofol for palliative sedation and achieved a rapid relief from severe symptoms such as pain, dyspnoea, and delirium. This is in accordance with the previous findings of propofol providing sedation and symptom relief in cases where midazolam does not provide sufficient symptom control.[19] The doses of propofol were in accordance with previously reported data[3] and confirmed a large interindividual variability in required dose. However, initial treatment success with sedation and symptom control did not guarantee uninterrupted sedation and good symptom control until death. In spite of continuous drug infusions, three of 14 patients had one or more episodes of spontaneous awakening and several patients required titration to high doses of propofol in order to maintain symptom control. These findings have two important clinical implications. The first is the importance of realistic information to patients and next of kin. If patients and next of kin are not warned that awakening might occur, such episodes might be interpreted as serious treatment failures. This aspect is particularly important because our qualitative data show that palliative sedation in most cases has been preceded by long lasting extensive suffering. Secondly this highlights the need for competent personnel who can monitor symptoms and level of sedation, and administer bolus doses and titrate infusion rates by need. In some hospitals this might only be feasible in an intensive or intermediate care unit, but our data demonstrate that it is also feasible at a palliative ward with trained staff. Our finding of patients experiencing spontaneous awakenings during ongoing sedation highlights the relevance of ongoing research on continuous monitoring of depth of sedation using bispectral index (BIS) or similar techniques.[20]

4.3 | Ethical issues

The study also raises an important ethical issue. Based on Norwegian recommendations sedation should as a main rule be paused for evaluation purposes.[18] Because such pausing of sedation was neither planned nor performed in any of the patients in the present study, we raise the question whether pausing palliative sedation should be the exception rather than the recommended rule. Thirteen out of fourteen patients died within2 days after start of palliative sedation with propofol, several patients required frequent bolus doses and repeated increases in propofol dose, several patients had stated a clear desire not to regain consciousness and the treating multidisciplinary team did not expect improvement in symptom burden in any of the included cases. Hence we would argue that reduction of the level of sedation should not be performed in patients who are imminently dying, when increased doses are needed, or against expressed wishes by patients or next of kin. Reduction of the level of sedation might be considered if the patient's clinical situation appears stable for several days and there during this time has been no need for bolus doses or increasing infusion rates.

It can be debated whether it is appropriate to apply jaw-thrust as a life-prolonging intervention in a patient receiving palliative sedation. On one hand, palliative sedation is not intended to hasten death but to provide symptom control until natural death.[21] For the physician it might cause moral distress if the patient dies as a direct consequence of the administration of a drug dose that in retrospect was too high, when a simple intervention could have prevented this. Further, abstaining from jaw-thrust might risk blurring the lines between palliative sedation and euthanasia in the public's perception, if patients are seen to die immediately after start of treatment. On the other hand, it can be argued that because hastening of death was not intended, no life-prolonging intervention should be performed in a terminal patient who does not want to regain consciousness.

4.4 | Weaknesses and limitations

The study's weakness is the limited number of patients. A larger number would have allowed more detailed statistical analyses and subgroup analyses. However, the validity of the main clinical and ethical issues raised by this study should not be influenced by the limited number of patients having received this treatment. A limitation regarding the qualitative data is the data source. One should keep in mind that the medical charts were not written for scientific purposes, and were influenced by a number of factors connected to medical tradition and local hospital culture.

5 | CONCLUSION

In conclusion this case series has confirmed that patients with severe suffering at the end of life can be successfully treated with propofol for palliative sedation. This can be performed in palliative medicine wards, but skilled observation and dose titration throughout the period of palliative sedation is necessary for uninterrupted sedation and symptom relief. Palliative sedation presupposes a profound understanding of the level of agony. The fact that severe suffering was repeatedly described in many of the patients several days before the initiation of palliative sedation, points at various physician barriers which delay the start of palliative sedation with propofol.

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CONFLICT OF INTEREST

The authors have no conflicts of interest.

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