Higher doses of opioids in patients who need palliative sedation prior to death: Cause or consequence?

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ARTICLE INFO

ABSTRACT

Background: Palliative sedation (PS) is necessary in a significant percentage of patients dying on an acute palliative care unit (PCU). Common indications are terminal restlessness, pain and dyspnoea. On our PCU, terminal restlessness was the main indication for PS but pain was the most prevalent symptom during admission. Because delirium is often drug induced in terminal cancer patients and opioids are amongst the most frequently implicated drugs, we hypothesised that the underlying pain problem and its treatment might have been related to the need for sedation.

Patients and methods: To test this hypothesis, we did a retrospective analysis on the use of medication with potential cognitive side-effects, focusing on analgesics, in 68 patients who died on the PCU after PS and 89 patients who died without PS.

Results: Ultimately sedated patients used opioids in significantly higher doses; they were more often treated with a rotation to another opioid and with amitriptyline. The dose of opioids used at various time points between admission and death was strongly related to the probability of PS.

Conclusions: Our findings support the hypothesis that, although pain was not the main indication for PS, pain and its treatment might have been primarily related to the need for palliative sedation in this patient cohort.

1. Introduction

Palliative sedation (PS) is the monitored use of medication intended to induce varying states of unconsciousness, but not death, in order to relieve refractory and unendurable symptoms in patients in whom death is imminent.[1] This implies that PS is only justified when unendurable symptoms are present that cannot be controlled with appropriate measures.

Common indications for PS are pain, terminal restlessness/delirium/confusion and dyspnoea. In some reported series delirium or confusion/restlessness was the most frequent indication for PS[2–4] whilst in other series dyspnoea[5,6] or pain[7–9] were found to be the most frequent indications.

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The practice of palliative sedation in our specialised unit for acute palliative care in a university cancer hospital in the Netherlands has been reported by Rietjens et al.[10] They described 157 patients who died at this unit, and studied differences between 68 sedated and 89 non-sedated patients. They found that terminal restlessness was the most common indication for PS (60%), followed by dyspnoea (46%) and pain (26%). Pain, however, was the most prevalent symptom on admission (up to 87%), and its prevalence remained high during admission – both for patients who died after PS as for patients who were not sedated before death. Prior to the onset of sedation, sedated patients more often suffered from delirium as compared to non-sedated patients at similar periods before death.

As it is known that delirium is often drug induced in advanced cancer patients and, more specifically, that opioids are amongst the most frequently implicated drugs,[11–14] it is possible that the underlying pain problem and its treatment were primarily related to the need for sedation. In this new retrospective analysis, we therefore studied differences in the use of medication with potential cognitive side-effects, with special attention for opioids and other, adjuvant, drugs used in the treatment of complex pain, between patients who were ultimately sedated prior to death and patients dying without sedation.

2. Patients and methods

We conducted a new retrospective analysis of data from the same cohort of patients that was studied by Rietjens et al.[10] The cohort consisted of all patients who died on our specialised acute palliative care unit (PCU) in a tertiary cancer hospital in Rotterdam, The Netherlands between October 2001 and October 2005.

The main goal during admission to the PCU is to provide symptom control for cancer patients with advanced disease. Daily multidisciplinary meetings are held with medical oncologists, nurses, an anesthesiologist, a neurologist and a psychiatrist present; other specialists are consulted when needed.

Pain is treated stepwise following the WHO pain medication ladder.[15] Of note, because many patients on the PCU are admitted with complex pain problems, high doses of opioids, opioid rotation, parenteral administration of opioids and/or adjuvant analgesics are often needed. In patients with severe pain, we generally use parenteral morphine or fentanyl for titration, if possible subcutaneously. Doses are titrated whilst closely monitoring the effect on pain and side-effects. Patients are monitored for the development of delirium using the Delirium Observation Screening (DOS) scale, a Dutch-developed 13 point nurse observation scale filled out three times daily.[16] For all patients who score ⩾3 points or when delirium is suspected on clinical grounds, the psychiatrist is consulted. In case of dose-limiting side-effects that cannot be controlled with symptomatic therapy and/or inadequate effect on pain, opioid rotation to another type of opioid is used. We reserve the use of parenteral hydromorphone for patients whose pain cannot be controlled with high doses of other opioids, when dose-limiting side-effects occur related to other opioids or when problems related to the administration of large volumes subcutaneously arise. In these circumstances, ketamine may also be used as an adjuvant drug.

A decision to use palliative sedation in a dying patient is discussed in a multidisciplinary meeting. In case of sedation, opioids are continued at the dose level used at the start of the sedation, according to (inter)national guidelines.

A detailed description of the data collection and analysis is given in the original article.[10]

In summary, the database was built in four time frames: admission (T0), 72–49 h before death (T1), 48–25 h before death (T2) and 24–0 h before death (T3). Baseline variables were scored on admission, other variables in the three time frames prior to death. The start of palliative sedation was not per se related to the time frames but could take place between admission and time of death.

Regarding medication, we studied the use of: acetaminophen/NSAIDs, opioids, ketamine, amitriptyline, anti-convulsants, corticosteroids, benzodiazepines, anti-hypertensive drugs, diuretics, anti-emetics and acid reflux/stomach medication. In the category of opioids we differentiated various types of opioids in the time frames prior to death and registered rotations to another type of opioid.

Per time frame, doses of all opioids administered (continuous, slow release and immediate release products) were recalculated to the morphine equivalent daily dose (MED) per 24 h. This was done according to published equianalgesic dose tables: oral morphine 60 mg/d = parenteral morphine 20 mg/d = transdermal fentanyl 25 mcg/h = parenteral fentanyl 25 mcg/h = oral oxycodone 30 mg/d = oral hydromorphone 8 mg/d = parenteral hydromorphone 4 mg/d.[17–19] Conversion rates for tramadol, methadone and epidurally or intrathecally administered opioids are not included in these tables. For tramadol we used a conversion rate of 4:1 (tramadol:morphine), according to results of a study by Wilder–Smith in 1994.[20] For oral methadone we used a conversion factor of 1:4.7 (methadone:morphine), according to data from a study by Walker et al.[21] For epidurally or intrathecally administered opioids no relevant studies could be found. We therefore decided to use conversion factors of 1:30 (epidural:oral morphine) and 1:300 (intrathecal:oral morphine), respectively, factors based on theory and clinical experience of pain specialists from the department of anaesthesiology in our hospital.

2.1. Statistical analyses

Data were analysed using STATA® version 10. Descriptive statistics were used to describe patients' characteristics. Reported p-values are two-tailed and $p < 0.05$ was considered to be statistically significant. To assess the association between the MED and the probability of PS logistical regression analysis was used. For each interval we calculated logistic regression of sedation (yes or no) versus log (MED). So, we obtained the probability of sedation for each MED-value and for all time periods.

3. Results

Patient characteristics of 68 sedated and 89 non-sedated patients are given in Table 1. In case of sedation, it was started in the last 24 h before death in a majority of patients (68%).

Table 1 – Patient characteristics.					
	Sedated patients N = 68		Non-sedated patients N = 89		p-Value
	N	%	N	%	
Male	31	46	40	45	0.87
Age median (range)	57	(27–89)	61	(25–80)	0.03
Primary tumour					
Lung	15	22	12	13	0.19
Gastro-intestinal	14	21	5	6	<0.01
Breast	11	16	22	25	0.16
Genito-urinary tract	7	10	17	19	0.13
Head and neck	5	7	5	6	0.66
Melanoma	8	12	6	7	0.27
Sarcoma	5	7	7	8	0.91
Other/(A)CUP	3	4	15	17	0.02

Symptom prevalence on admission and the indications for palliative sedation are shown in Table 2. There was a high prevalence of pain in both groups.

One patient in the sedated group was excluded from further analyses, because no information on used medication could be found.

No statistically significant differences were found in the percentage of patients using anti-convulsants, corticosteroids, anti-hypertensive drugs, diuretics, anti-emetics and acid reflux/stomach medication in T0-T3. Significantly more patients in the ultimately sedated group used benzodiazepines at T0, 10/68 (22%) sedated versus 2/89 (3%) non-sedated patients ($p = 0.002$). For T1–3 data could not be used as the indication for benzodiazepines was not registered, so they could then also be used for the purpose of PS.

The use of pain medication is shown in Fig. 1. No significant differences were found in the percentage of patients using WHO step 1 pain medication and opioids (Fig 1a). The figure shows that the percentage of patients using WHO step 1 medication decreased with time, whilst the percentage of patients using opioids increased in both groups.

Fig. 1b shows that sedated patients more frequently used amitriptyline in T0–2. ($p = 0.02$, $p = 0.002$, $p = 0.004$, respectively). Between T0 and T1 the percentage of patients using ketamine in the ultimately sedated group increased from 4.5% to 13.4%, whereas it remained stable in the non-sedated group (differences NS).

Fig. 1c shows that about 40% of the ultimately sedated patients used haloperidol in T1 and T2, whereas this percentage was about 20% for the non-sedated group ($p = 0.02$ and $p = 0.034$, respectively).

Variations regarding the use of specific types of opioids and the various routes of administration were studied per time frame. At T0, patients from the ultimately sedated group and the non-sedated group used similar types of opioids. Many patients were rotated from oral to parenteral opioids during admission, but especially between T0 and T1, without differences between the groups. Between T0 and T1, rotation to another type of opioid was more often used in the group of patients who were ultimately sedated than in the non-sedated group: in 30/68 pts (44%) and 19/89 pts (22%), respectively ($p < 0.005$). In particular, more patients were set on hydromorphone (9.3 versus 1.2%, $p = 0.017$) or spinal pain medication (4.5 versus 1.2%, NS) during this period. There were no significant differences in the use of opioid rotations between sedated and non-sedated patients during the last 72 h of life.

The median morphine equivalent daily dose (MED) of opioids in T0–3 for sedated and non-sedated patients is shown in Fig. 2. Sedated patients used significantly higher doses of

| Table 2 – Symptom prevalence on admission and indications for palliative sedation (Main results of previous analyses).					
	Sedated patients N = 68	%	Non-sedated patients N = 89	%	p-Value
Symptom prevalence on admission					
Pain	59	87	69	78	0.2
Dyspnoea	20	29	28	31	0.7
Delirium	8	12	9	10	0.8
Anxiety	6	9	6	7	0.7
Indication for palliative sedation					
Pain	18	26	–	–	
Pain as the only indication for PS	7	10	–	–	
Terminal restlessness	41	60	–	–	
Dyspnoea	31	46	–	–	
Other	10	15	–	–	
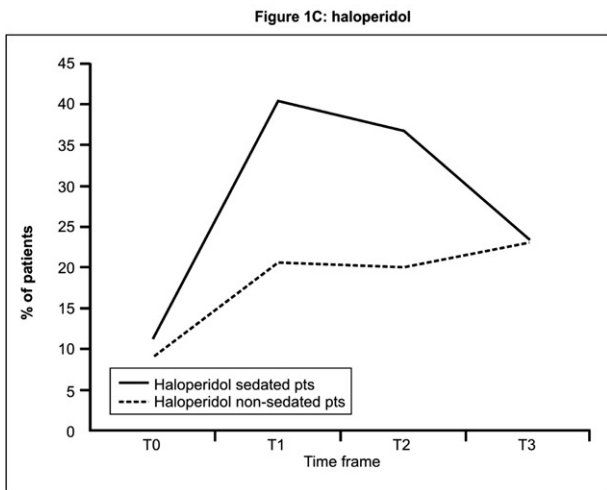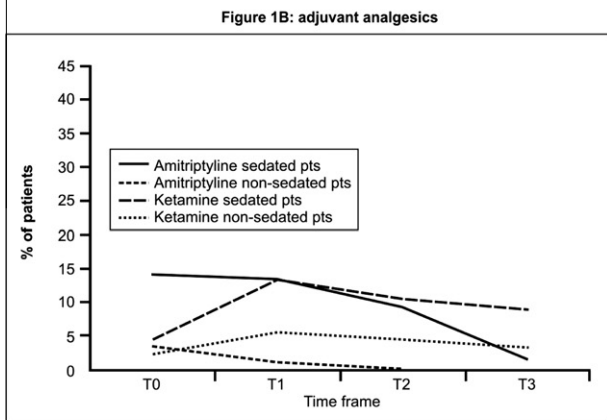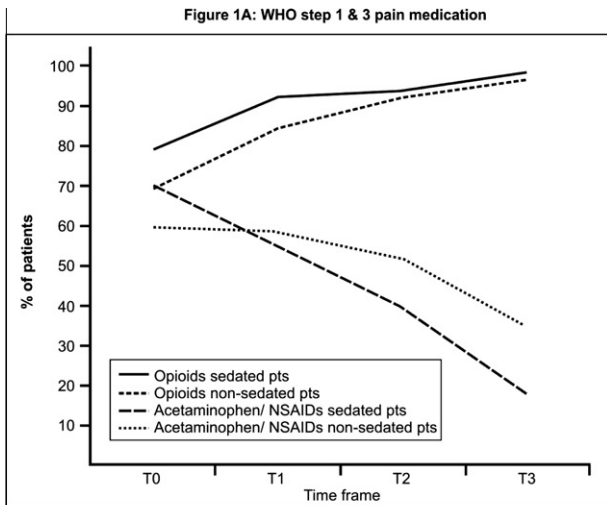
Fig. 1 – Differences in the use of pain medication and haloperidol between sedated and non-sedated patients.
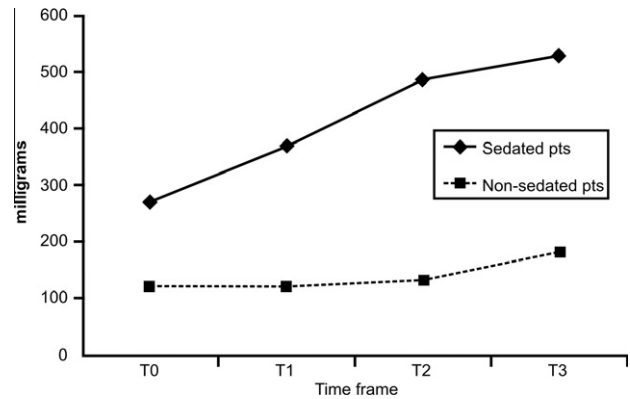

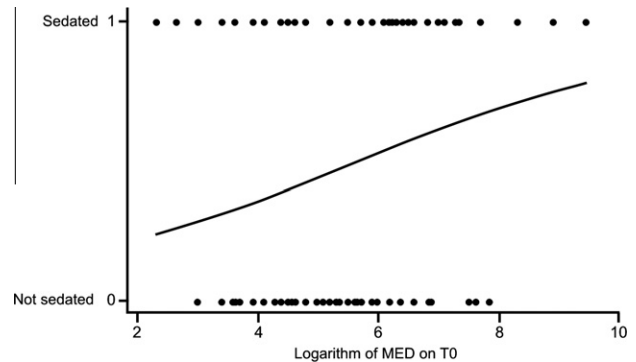Fig. 2 – Median equianalgesic dose of opioids per time frame.

Fig. 3 – Probability of PS in relation to the MED of opioids on T0, logistic regression analysis.

regression analysis. The figure shows that there was a strong relationship between the dose of opioids at T0 and the probability of becoming sedated before death ($p = 0.017$). Similar results were obtained for time frames T1 and T2 ($p = 0.004$) and $p < 0.001$).

4. Discussion

PS is necessary in a significant percentage of patients dying on an acute PCU.[3,5] These patients suffer from treatment refractory symptoms distressing them as well as their family members and care givers. The setting in which PS is performed, is therefore always difficult and stressful, making it all the more important to better understand the trajectory leading to PS and the factors that may influence it.

As mentioned in the introduction of this article, in some settings delirium or terminal restlessness/confusion is the main indication for PS whilst in others dyspnoea or pain is the main indication. To our knowledge, studies on predictors for the occurrence of refractory symptoms in the dying phase have not been performed.

In our cohort of patients pain was one of the main indications for PS in 26% of patients, and the only indication in 10% of patients – although pain was very prominent. This reflects the fact that we have the facilities and the experience to treat patients with severe and difficult pain problems. However, pain

opioids in all time frames ($p = 0.025$, $p = 0.001$, $p < 0.001$, $p < 0.001$, respectively).

One patient was found to use extremely high doses of opioids. Because the possibility of an error in noting the dose could not be excluded, this patient was excluded for the analyses on equianalgesic doses of opioids.

Fig. 3 shows the probability of dying with PS in relation to the logarithm of the MED of opioids at T0 using logistic

and its treatment might very well be indirectly related to the need for PS as it is known that delirium is often drug induced. Because in our cohort of patients, delirium/terminal restlessness was the main indication for PS, we studied differences in medication with potential cognitive side-effects between ultimately sedated patients and non-sedated patients. We found some striking differences in the use of pain medication. The ultimately sedated patients used opioids in significantly higher doses; they were more often treated with a rotation to another type of opioid – in some to hydromorphone – and with adjuvant amitriptyline. Furthermore, ketamine and spinal medication were used more frequently, although differences were not statistically significant. These results support our hypothesis of more difficult pain problems in the ultimately sedated group compared to the non-sedated patients. Although it is likely that sedated patients had more severe pain, we unfortunately have no data to substantiate this as the severity of pain was not registered in the database in this study period. However, in our previous analyses in this same group of patients we already found indications to suggest a more aggressive course of the underlying cancer in the sedated patients, which is also compatible with the assumption of more difficult pain problems in this group of patients.[10] Thus, ultimately sedated patients are likely to have had more difficult pain problems, leading to more intense treatment with a higher risk of terminal restlessness/delirium.

Differences in pharmacokinetics and pharmacodynamics of pain medication between the groups may also be important. It is possible that ultimately sedated patients had less analgesic effects and/or more side-effects from the used medication. Large inter-individual differences in the metabolism of morphine have indeed been described[22,23] and genetic variability is assumed.[24] Results of studies on the relation between morphine metabolites and delirium in cancer patients are conflicting, however.[25–28] Furthermore, a recently published large European study could not find an association between genetic variability and opioid dose.[29] More research on the effects of pharmacokinetic and pharmacogenetic variability on analgesic and side-effects of opioids is needed.

To our knowledge, this is the first study addressing the possible role of pharmacological interventions for the treatment of complex pain in the need for PS in a group of terminally ill cancer patients. Although the retrospective design of our study is an important limitation, our findings indicate that more insight in the pathophysiologic mechanisms of refractory symptoms in the dying phase is needed.

In conclusion, our findings suggest that ultimately sedated patients had more difficult pain problems and/or had a disturbed dose–effect relationship for opioids. The more intensive treatment of these patients could have led to a higher rate of treatment refractory delirium/terminal restlessness, sometimes necessitating PS. Although pain was not the main indication for PS in our cohort of patients, its treatment might very well have been related to the need for PS. This emphasises the need for more individualised treatment schemes, to minimise the risk of adverse events.

Conflict of interest statement

None declared.

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