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The Use of Opioids in the Last Week of Life in an Acute Palliative Care Unit

Sebastiano Mercadante, MD[1,2], Patrizia Ferrera, MD[1], and Alessandra Casuccio, BS[3]

Abstract

The aim of this survey was to assess the opioid use in the last week of life of cancer patients admitted at an acute palliative care unit. From a consecutive sample of patients surveyed for a period of one year, patients who died in the unit were selected. Type of opioid, route of administration, and doses were recorded one week before death (or at admission time if the interval admission-death was less than one week) (−7), and on the day of death (Tend). Seventy-seven patients died in the unit in the period taken into consideration (12.4%). Oral morphine equivalents were 170 mg/day and 262 mg/day at −7 and Tend, respectively. Patients were receiving transdermal drugs or intravenous morphine at Tend, with a trend in the use of intravenous morphine at Tend ($p=0.07$). Intravenous morphine was more frequently used in sedated patients at Tend ($p=0.015$).No differences in age, gender, opioid doses, and OEI were found among opioids used. In patients who were sedated doses of opioids were significantly increased ($p=0.012$). In the last week of life intravenous morphine is the preferred modality to deliver opioids in an acute palliative care unit. Doses increases prevalently observed in sedated patients were performed before starting sedation with the purpose to treat concomitant distressing symptoms, such as dyspnoea.

Keywords

opioids, end of life, intravenous morphine

Introduction

Opioid use is of paramount importance to relieve cancer pain, particularly when death is approaching. Controversies surrounding the risks, the benefits, and ethical foundation for the use of opioids at the end of life have been discussed extensively in both the ethical and medical literature. Opioids have become tainted with the implication that they hasten death, although studies have found a lack of association between opioid dose or incremental opioid dose and length of survival in patients with advanced cancer, close to death.[1-3] There is a great variability among patients with advanced cancer in the experience of pain of the last days of life.[4] Pain and symptoms may become more severe as death approaches, explaining the use of higher doses of opioids.

Mean doses of opioid used at the time of death varied widely between studies, and different pain trajectories have been described. In some cases, a crescendo of pain has been reported,[4] whereas in other situations, pain remains stable or tends to diminish in the last days to weeks, as reported in different settings.[5-7] However, opioids can be indicated to treat intractable dyspnoea, generally at higher doses in comparison with doses required for pain relief, and in a clinical scenario, it is often difficult to distinguish "how much" is given for one indication or for another one. Information regarding the use of opioids in the last week of life in an acute palliative care unit is lacking. As a part of a secondary analysis of a previous survey,[8] we analyzed the pattern of opioid use in the last week of life in patients with advanced cancer, who died after admission to an acute palliative care unit.

Patients and Methods

The protocol study was approved by the ethical committee of the University of Palermo, and informed consent to use the data was obtained from relatives. From a consecutive sample of patients with cancer admitted to an acute palliative care unit for a period of 1 year, patients who died after admission were included in this survey. Basic information was recorded, including tumor diagnosis, age, and gender.

[1] Pain Relief and Palliative Care Unit, La Maddalena Cancer Center, Palermo, Italy
[2] Palliative Medicine Teaching, University of Palermo, Palermo, Italy
[3] Department of Clinical Neuroscience, University of Palermo, Palermo, Italy

Corresponding Author:
Sebastiano Mercadante, Pain Relief and Palliative Care Unit, La Maddalena Cancer Center, Via San Lorenzo 312, 90146 Palermo, Italy.
Email: terapiadeldolore@lamaddalenanet.it

Table 1. Characteristics of Patients and Doses of Opioids Expressed as Oral Morphine Equivalents

Patients	77
Age (years)	62.5 (95% CI 59-65)
Gender, M/F	48/29
Sedation	42/77
Patients receiving opioids at T−7/Tend	58/61
Oral morphine equivalents at T−7 (mg)	170 (95% CI 118-222)
Oral morphine equivalents at Tend (mg)	262 (95% CI 130-394)[a]
OEI%	8.4 (95% CI 3-14)
OEI mg	13.3 (95% CI 3-23)

[a] T−7 versus Tend: $P = .040$. Opioid escalation index (OEI)% and OEI mg.

Opioid therapy, including type of opioids, dose, and route of administration, prescribed 7 days before death (−7) and the same day of death (Tend) were recorded. If survival was less than a week, data for −7 were recorded on the day of admission. Number of patients who required sedation before death was also recorded.

Opioid escalation index (OEI), in milligrams or as percentage, was calculated from the initial dose at −7 until Tend, according to the following formula:

$$\text{OEI\%: } [(x - y)/y]/\text{days} \times 100,$$

where x is the last dose before death and y is the dose at −7, both expressed as equivalents of oral morphine, and OEI mg is $(x - y)$/days.[9] Oral morphine equivalents were calculated according to department policy,[10] the conversion ratios used among opioids and routes of administration being the following: oral morphine 100 = intravenous morphine 33 = transdermal (TTS) buprenorphine 1.3 = TTS fentanyl 1 = intravenous fentanyl 1 = oral methadone 20 = intravenous methadone 16 = oral oxycodone 70, transdermal buprenorphine 1.3.

Statistical Analysis

Data were collected and analyzed by the Statistical Package for the Social Sciences (SPSS) Software 14.0 version (SPSS, Inc, Chicago, Illinois). Statistical analysis of quantitative data, including descriptive statistics, was performed for all the items. Frequency analysis was performed using chi-square test. The paired samples Student t test was used to compare the differences in opioid doses at the time intervals. The 1-way analysis of variance (ANOVA) was used to compare the different parametric variables. All P values were 2-sided and P values less than .05 were considered to indicate statistical significance.

Results

A total of 77 patients died in the unit in the period taken into consideration (12.4% of 618 admissions recorded in 1 year). At −7, 58 patients were receiving opioids at a mean oral morphine equivalent dose of 170 mg/d. Doses significantly increased up to 262 mg/d before death ($P = .040$; see Table 1). While only about 15% of patients were still receiving oral opioids at −7, almost all patients were receiving transdermal drugs or intravenous morphine at Tend. There was a trend in the use of intravenous morphine at Tend ($P = .07$), which was significant in sedated patients ($P = .015$). Number of patients receiving the different opioids are presented in Table 2.

Table 2. Number of Patients Receiving Different Opioids and Route of Administration at T−7 and Tend

	OS	TTS	IV	IT	Total
T−7					
Oxycodone paracetamol	2	0	0	0	2
Morphine	1	0	19	1	21
Methadone	2	0	4	0	6
Fentanyl	0	10	0	0	10
Oxycodone	6	0	0	0	6
Buprenorphine	0	13	0	0	13
Total	11	23	23	1	58
Tend					
Tramadol	0	0	1	0	1
Morphine	1	0	30	1	32
Metadone	0	0	4	0	4
Fentanyl	0	9	0	0	9
Oxycodone	2	0	0	0	2
Buprenorphine	0	14	0	0	14
Total	3	23	34	1	61

Abbreviations: IV, intravenous; IT, intrathecal; OS, oral; TTS, transdermal.

In all, 42 patients required terminal sedation, mainly with midazolam. About 80% of these patients were receiving opioids. No differences in age ($P = .227$), gender ($P = .699$), opioid doses at T0 ($P = .912$), opioid doses at Tend ($P = .826$) were found between patients who were sedated and patients who were not sedated. Sedated patients had an admission time longer than patients who were not sedated ($P = .005$). Changes in opioid doses were found between T−7 and Tend. In patients who were sedated, doses of opioids were significantly increased ($P = .012$), whereas no significant changes were found in nonsedated patients ($P = .274$).

Discussion

This survey showed that patients close to death present complex problems requiring different approaches with opioids in terms of doses and routes of administration, according to clinical individual needs. The findings of this study confirm the peculiarity of this phase in patients admitted in an acute pain relief and palliative care unit. As expected, intravenous morphine was most frequently used at time of death, particularly in patients who required sedation. This route is preferred in our acute palliative care unit because it warrants a prompt and predictable effect. Alternatively, transdermal drugs were frequently used, because most patients were unable to swallow. Opioid doses increased, particularly in patients who were then sedated, possibly to treat other symptoms, like dyspnoea.

Mean doses of opioids used at the time of death vary widely between studies, ranging from 59 to 659 mg with an average of

192 mg of morphine, with doses in North America being the highest than elsewhere.[11] In a recent retrospective analysis of intravenous morphine patient-controlled analgesia in home care patients, opioid doses remained stable, in the range of 96 to 115 mg/d, in the last week of life, although the use of such a technique is questionable in severely ill patients.[12] In a hospice setting in United Kingdom, lower doses of opioids were used in the last week of life. The mean daily opioid dose increased from 42 to 55.5 mg over the last 7 days of life, with an increase in the number of patients receiving opioids from 61% at admission up to 89%. Marked increases in opioid doses were not associated with survival, were more likely to be given for pain, and were often associated with the use of sedatives. Of interest, such increases were no more likely to occur in the last 48 hours of life than earlier.[3] The proportion of patients requiring high doses of opioids close to the end is commonly relatively low. Only 7% to 12% of patients required doses of more than 300 mg of morphine.[2-13]

Unfounded concerns about the possible life-shortening effect of opioids may result in less than optimal symptom management in end-of-life care.[14] Some studies have examined the relationship between the use of opioid and survival but none of them reported that opioids had shortened life. In a survey of a hospice population, the final opioid dose, but not percentage change in dose, was only one of the several factors associated with a shorter survival.[1] No differences in survival between patients receiving high doses and those receiving low doses have been found.[13] In a group of patients receiving relatively high doses of opioids, an increased survival was found in patients who were on 300 mg/d or more of oral morphine equivalents.[15] In previous studies, no significant differences in survival were found in patients who received higher doses of opioids[2] and opioid doses were mainly found unchanged after starting sedation,[5,16] mostly lower than 300 mg of oral morphine equivalents, suggesting that this drug class was administered with the purpose of providing analgesia, rather than sedation.[2,17]

In this survey, 47 patients increased their opioid doses, 27 patients did not change opioid doses, and in 3 patients, opioid doses were decreased, although minimally. High doses were relatively more frequent: 13 patients (16.8%) received oral morphine equivalents of more than 300 mg, most of them being sedated patients (12.9%). Moreover, the number of patients receiving opioids at admission was higher than in previous hospice experiences.[3] Opioid doses significantly increased in the last week of life, with an OEI% of 8.4. However, whereas no significant changes in opioid were found from −7 to Tend in nonsedated patients, opioid doses increased significantly in the group of patients who were sedated. This could reflect the selectivity of patients admitted in an acute palliative care unit and the use of opioids for other purposes, like dyspnoea. Treating dyspnoea, in fact, commonly requires higher doses in patients receiving opioids for their pain. Of interest, 8 patients requiring high doses were already receiving such doses at −7. In fact, in the primary analysis, these increases in opioid doses were minimal in the interval between starting sedation and death, on average 24 hours.[16] Agitated delirium, dyspnoea, and existential distress are the most common problem requiring sedation,[5,18,19] while pain is hardly a unique indication to sedate or is associated with other manifestations of suffering. Thus, the increase in opioid doses could be partially attributed to the large number of patients presenting dyspnoea in the sedated group of patients, in an attempt to treat dyspnoea before starting sedation. In this context, in fact, opioids were not given for sedating purposes, as the level of consciousness was modulated by midazolam.[14] Opioid administration should be continued once sedation is initiated, as there is no tangible evidence that patients do not experience pain. Regretfully, opioids have been found to be administered alone as sedative agents in general practice.[20-22] Concerns were also reported in other multicenter surveys where a small number of patients experienced fatal complications related to sedation.[19]

There are some limitations in the interpretation of the results of the current study. The need of increase in opioid dose is difficult to discern in a clinical scenario, when opioids are used for different indications, for example pain and dyspnoea. Furthermore, these findings cannot be generalized due to the characteristics of the unit, the selected population, and the level of monitoring and medicalization described elsewhere.[23] However, the aim of the study was exactly to describe what occurs in an acute pain relief and palliative care unit, which is relatively less frequently reported in the literature where data gathered from hospice and home care settings prevail.

In conclusion, in an acute setting, patients close to death present complex problems requiring different approaches with opioids in terms of doses and routes of administration, according to different clinical circumstances. Intravenous morphine was most frequently used at time of death. Alternatively, transdermal drugs were most frequently used, because most patients were unable to swallow. Opioid doses changed in the last week of life, with increases more frequently observed in patients who were subsequently sedated, possibly in an attempt to treat dyspnoea.

Declaration of Conflicting Interests

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