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ORIGINAL RESEARCH

The Use of Opioids in an Acute Palliative Care Unit to Re-assess Prescriptions

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ABSTRACT

***Introduction*:** This study aimed to re-assess opioid prescriptions in an acute palliative care unit (APCU) 12 years after a previous audit.
***Methods*:** Consecutive patients with advanced cancer who were admitted to the APCU for a period of 5 months for uncontrolled pain were analyzed. Information regarding opioids, and route of administration, prescribed prior to admission, during admission, and at time of discharge was recorded. Opioids, doses, and routes were changed according to the clinical need to obtain the maximum benefit, individualizing the treatment. The opioid escalation index was calculated in milligrams (OEImg) and as a percentage (OEI%).
***Results*:** A total of 113 patients were assessed. The mean pain intensity at admission and at time of discharge was 6.4 (SD 1.8) and 2.3 (SD 1.4), respectively ($P < 0.0005$). The mean opioid dose expressed as oral morphine equivalent (OME) by patients who were receiving opioids before admission was 128 mg/day (SD 120). There was no statistical difference in OME between admission and discharge time. Sixty-one and 20 patients were prescribed a second and a third opioid/route, respectively. Mean OEI% and OEImg were 9.3% (SD = 22.5) and 4.0 mg/day (SD = 24.1), respectively. Only a minority of patients had a breakthrough pain prescription at admission. Intravenous morphine was more frequently prescribed at beginning, then replaced by oral morphine and fentanyl preparations at discharge.
***Conclusions*:** An intensive and careful use of opioids in the APCU allows for the achievement of adequate analgesia in all examined patients within a short time, without increasing OME. These findings should encourage further studies in APCUs as well as in other palliative care settings.

Keywords: Cancer pain; Palliative care; Opioids; Acute palliative care unit

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Key Summary Points

Why carry out this study?

Information regarding the use of opioids in acute palliative care units (APCU), where more resources and experience are available, is poor. The study addressed the use of opioids in an acute palliative care unit after an audit published 12 years ago.

What was learned from the study?

A careful use of opioids allows for effective pain control in all patients without increasing doses, as expressed in oral morphine equivalents, within the framework of comprehensive palliative care management.

INTRODUCTION

Pain is one of the most prevalent and feared symptoms reported by patients with advanced cancer. Pain is experienced by at least 30% of patients undergoing an oncological treatment for metastatic disease and by more than 70% of advanced cancer patients [1].

The application of WHO guidelines has been reported to achieve satisfactory pain relief in up to 90% of patients with cancer pain using simple measures, even in home settings [2]. However, some patients may experience insufficient pain relief as a result of the underuse of opioids. Mean doses of opioids vary widely between settings due to different populations examined, generally at home, oncologic ward, hospice, or outpatient clinic. In a cross-sectional survey of more than 3000 patients, among 143 palliative care centers in various European countries, only a minority of the patients who used opioids were receiving high doses. About 75% of patients receiving morphine were treated with doses less than 150 mg/day [3]. This observation allows for an uncertain interpretation: either the majority of patients are adequately treated with low to moderate opioid doses, or the prescribed doses were insufficient for those requiring higher-end dosage ranges. Pioneering studies have reported that the proper use of higher opioid doses is both safe and effective when administered by skilled professionals [4, 5]. Patients are often referred to specialistic centers for uncontrolled pain from any setting or stage of disease. The acute pain relief and palliative care units (APCU) have been differently described in the literature [6]. These units are characterized by the admission of patients with advanced cancer for pain and symptom management during all the trajectory of disease, including patients who are still receiving active treatment of disease and not only at the end of life. In a study performed more than 10 years ago, data showed that an intensive approach was able to resolve distressing situations in a short time by optimizing the use of opioids [7]. Since then, APCU activities have been implemented with more beds available and a more intensive collaboration with oncologists. Moreover, a hospice with ten beds, adjacent to the unit, was added to accommodate patients who cannot be discharged due to the complexity of their treatment or unresolved social issues [8]. The aim of this study was to evaluate opioid prescriptions in an APCU 12 years after a previous audit.

METHODS

This is a prospective study of a sample of consecutive patients with advanced cancer who were admitted to the APCU for a period of 5 months. This was a pre-planned secondary analysis of a study assessing pathways and functioning of an APCU. Informed consent was obtained. The study was approved by the provincial ethical committee of Palermo. Patients' data were anonymized. The activity of APCU has been described elsewhere [9]. Briefly, other than providing medical treatment of pain and symptoms, time is spent for communication, education, and psychological care, particularly focusing on the individual needs, globally expressed by comprehensive palliative care management. The choice of drugs and route of administration, including the need for opioid switching, was determined on an individual basis by the attending physician and discussed during bi-daily clinical

rounds with the supervisor. Once the most stable condition possible is reached, patients are discharged home or assigned to a specialized home care program. Patients with unfavorable clinical conditions, who also face social challenges that limit home care options, are transferred to the adjacent hospice on the same floor, where they remain under the care of the same team.

Inclusion criteria were uncontrolled pain (≥ 4 on a numerical scale 0–10), an opioid prescription, and a sufficient cognitive function (MDAS ≤ 7), allowing a proper assessment were selected for this study. Exclusion criteria were a short life expectancy because of confounding factors such as symptom hyper-expression occurring in the last days of life would have influenced the outcome and death during admission [10].

Basic information, including tumor diagnosis, age, and gender, was collected. Opioid therapy, including type of opioids, the maximum dose achieved with each opioid, and route of administration, prescribed prior to admission, during admission, and at time of discharge was recorded. According to local policy, opioids were administered with the aim of achieving adequate pain relief (with an approximate intensity of ≤ 4 on a numerical scale from 0 to 10), a limited number of breakthrough pain (BTP) episodes (three episodes per day or less), and an acceptable level of adverse effects intensity. Comprehensive palliative care was offered.

Opioids, doses, and routes were changed according to the clinical need to obtain the maximum benefit, individualizing the treatment. Opioid/route switching was performed by using initial conversion ratios previously described. For each opioid prescription, the maximum dose of each opioid was recorded, expressed as oral morphine equivalents (OME). OME was calculated according to department policy [11]. Opioid escalation index (OEI), in milligrams or as percentage, was calculated from data recorded at admission and at discharge, according to the following formula: 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 OME; and OEImg is $(x-y)/\text{days}$ [12]. The protocol study was approved by the provincial ethical committee of Palermo. This study was performed in accordance with the Helsinki Declaration of 1964 and its later amendments. Patients' informed consent was obtained.

Statistical Analysis

Frequency analysis was performed by the chi-square test or Fisher's exact test, as appropriate for categorical variables, and the independent Student's t test for continuous parameters. The paired-sample Student's t test was used to compare the differences in opioid doses at the time intervals. Data were analyzed using IBM SPSS Statistics, version 24 (IBM Corp., Armonk, NY, USA). All P values were two-sided, and a P value of less than 0.05 was considered statistically significant.

RESULTS

Two-hundred nineteen patients were admitted to APCU in the period taken into consideration. Twenty-seven patients died during the admission. One-hundred-thirteen patients (51%) presented with uncontrolled pain and were taken into consideration for analysis.

The mean age was 65.3 years (SD 11.4), and 53 (46.9%) patients were males. The majority of patients had a Karnofsky of 40–50. The primary diagnoses were in a rank order: lung (n = 50), gastrointestinal (n = 18), urogenital (n = 16), breast (n = 12), pancreas (n = 6), and others (n = 11). The median duration of admission was 7 days (SD 3.0). Eighty patients were discharged home. Twenty-six patients were transferred to hospice, four to the oncology unit, two to a long-term care unit for rehabilitation, and one to neurosurgery. The mean pain intensity at admission and at time of discharge was 6.4 (SD 1.8) and 2.3 (SD 1.4), respectively. The difference was statistically different (P < 0.0005).

At admission, 77 of 113 patients were receiving some analgesic therapy, including non-opioid and opioid analgesics, unsuccessfully. The mean opioid dose expressed as OME by patients who were receiving opioids before admission was 128 mg/day (SD 120, range 15–600 mg).

Table 1 Number of patients who were prescribed opioids and route of opioid administration

No. of patients	Admission		1° opioid		2° opioid		3° opioid		Discharge	
	77		101		61		20		95	
	No.	mg/day	No.	mg/day	No.	mg/day	No.	mg/day	No.	mg/day
BUP TD	3	56 (55)	5	124 (138)	8	88 (33)	3	65 (23)	13	100 (87)
FENT TD	24	200 (113)	6	110 (124)	8	94 (113)	1	60 (–)	10	126 (160)
ME iv	1	600 (–)	12	194 (76)	4	232 (121)	2	435 (233)	1	150 (–)
ME os	7	212 (101)	9	343 (246)	14	168 (103)	9	183 (116)	18	197 (173)
MO os	14	75 (68)	15	41 (47)	17	99 (145)	4	105 (57)	35	74 (109)
MO par (Iv-sc)	4	116 (76)	43	124 (143)	9	165 (127)	1	360 (–)	8	246 (400)
OX–N os	11	50 (32)	–	–	–	–	–	–	1	30 (–)
OX–paracetamol	4	23 (6)	2	79 (80)	–	–	–	–	1	135 (–)
TAP	6	45 (30)	9	38 (26)	1	–	–	–	8	39 (24)
Codeine-paracet	2	60 (0)	–	–	–	–	–	–	–	–
Paracet	–	–	–	–	–	–	–	–	–	–
Tramadol	1		–	–						
2 opioids, routes										
BUP TD			–	–	–	–	2	75 (63)	–	–
FENT TD			–	–	–	–	2	254 (319)	1	65 (–)
ME iv			–	–	1	180 (–)	–	–	–	–
ME os			–	–	–	–	–	–	1	45 (–)
MO os			1	100 (–)	3	24 (15)	–	–	3	24 (16)
MO par (Iv-sc)			2	90 (64)	1	9 (–)	–	–	–	–
OX–paracet			1	30 (–)	–	–	–	–	–	–
TAP			–	–	–	–	–	–	–	–
Total OME (mean)	77	128 (120)	101	133 (155)	61	134 (121)	20	211 (176)	95	120 (172)

Drugs: *BUP TD* transdermal buprenorphine, *FENT TD* transdermal fentanyl, *MO os* oral morphine, *MO par* parenteral morphine, *ME os* oral methadone, *ME iv* intravenous methadone, *OX* oral oxycodone, *TAP* tapentadol, *OME* oral morphine equivalents. Below data regarding the second opioid added to the basic opioid prescription (in case of combination of two opioids)

One-hundred-one patients (89%) were prescribed a new line opioid therapy at regular intervals after APCU admission, either for opioid-naïve patients or those receiving opioids, generally after an initial intravenous opioid dose titration. Drugs, doses, and route of administration changed after the first opioid prescription, as well as the maximum dose of each drug, expressed as OME are shown in Table 1.

Sixty-one and 20 patients were prescribed a second and a third opioid/route, respectively. Patients who were prescribed a third line treatment resulted to receive the highest OME doses (211 mg/day; SD 176) ($P<0.05$). A minority of patients were prescribed a combination of opioids.

Twenty of 101 patients (20%), 13/61 (21%), and 8/20 (40%) patients were receiving more than 200 mg of oral morphine equivalents, as maximum dose of the first, second, and third opioid prescription, respectively. The mean OEI% and OEImg calculated from pre-admission OME and discharge OME, excluding those who were no receiving opioid therapy at admission) were 9.3% (SD = 22.5) and 4.0 mg/day (SD = 24.1), respectively.

The mean final dose of opioids at time of discharge, expressed as OME, for all patients was 120 mg/day (SD 172). There was no statistical difference between OME prescribed as first line at admission and at discharge ($P=0.329$). Older patients (>65 years) received lower opioid doses expressed as OME in comparison with adults at the first opioid prescription ($P=0.007$), at the second one ($P=0.006$), at the third one ($P<0.05$) and at discharge ($P<0.0005$). No gender differences were found at any opioid therapy interval ($P>0.05$).

Only a minority of patients had a BTP prescription at admission (not reported in Table 2). After being admitted, a large number of patients were prescribed a BTP medication, the pattern of which changed during admission. While intravenous morphine initially prevailed, at discharge oral morphine and fentanyl preparations were the most frequent BTP medications. Intravenous morphine was maintained in a certain number of patients who were subsequently transferred to hospice.

Table 2 Prescription of BTcP medications and doses (mean, SD)

	1° BTP med		2° BTP med		3° BTP med		BTP med at discharge	
	No.	mg/day(SD)	No.	mg/day (SD)	No.	mg/day (SD)	No.	mg/day (SD)
No. of patients	104		35		13		97	
ME iv	9	4.3 (14)	2	4.2 (0)	2	5.4 (51)	1	3 (–)
ME os	1	30 (–)	2	50 (0)	1	25 (–)	2	40 (0)
MO os	16	7 (9)	4	6 (7)	2	13 (11)	50	8 (10)
MO IV	70	14 (12)	11	20 (10)	1	150 (–)	16	29 (46)
SLF	8	225 (119)	14	227 (138)	7	231 (144)	19	173 (137)
FBT	–	–	2	50 (14)	–	–	6	230 (267)
OTFC	–	–	–	–	–	–	2	100 (0)
FPNS	–	–	–	–	–	–	1	100 (–)

Drugs: *MO os* oral morphine, *MO par* parenteral morphine, *ME os* oral methadone, *ME iv* intravenous methadone, *SLF* sublingual fentanyl, *OTFC* oral transmucosal fentanyl citrate, *FPNS* fentanyl pectin nasal spray. For fentanyl preparations, doses are in mcg (mean, SD)

DISCUSSION

This study provided interesting information about opioid prescription in an APCU. As in the previous audit, many patients required complex treatments during admission with different lines of opioids and changes in drugs and route to achieve the optimal balance between analgesia and adverse effects in the context of a comprehensive palliative care management. Most patients were undertreated prior to admission, although OME at admission for patients prescribed opioids was three times higher, compared to a precedent survey [7], probably due to natural selection of patients admitted to the APCU in this last years. A significant change in symptom intensity was observed after few days in an APCU [13].

In different palliative care settings patients with moderate and severe pain required a significantly longer time to achieve stable pain control. The method of titration and consequently the median length of time to achieve stable pain control in patients with moderate–severe pain required a median of 8–22 days, with small dose increments of opioids [14]. Original data from these studies, however, showed that undertreatment in the longitudinal part of the study strongly biased the outcome, as treatments were nonstandardized and probably non-optimized, confirming the poor quality of care, despite being performed in some palliative care settings [15]. Indeed, although high levels of pain intensity, often due to previous undertreatment, were predictive of more complex analgesic treatment, pain control was achieved in a very short time [16]. One can argue that an intensive and experienced approach allows a better achievement of adequate analgesia in comparison with other settings.

Most patients required a rapid intravenous opioid dose titration, as evidenced by the large use of intravenous morphine in the first instance, also explaining why intravenous morphine was used as BTP medication first, probably to assist initial dose titration. Differently from what we reported in a previous study, however, OME did not change compared to initial doses, at least for patients who received opioids at admission. Only 20–40% of patients received doses higher than 200 mg/day of OME. In a secondary analysis, in which OEI% was used as a surrogate marker for opioid responsiveness, approximately 44% of patients with cancer pain had an OEI% > 5%. There were no significant associations between OEI% and age, neuropathic pain, incident pain, psychological distress, or addictive behavior [17]. However, OEI indexes are monitoring instruments and not outcome measures as erroneously interpreted.

In this study OEI indexes, that express the need of rapid dose escalation to achieve adequate analgesia, were relatively low. This could be attributed to major experience acquired in recent years to optimize opioid response. This data is consistent with the findings of a similar APCU, where about half of patients achieved analgesia without OME increase [18]. A multidimensional palliative care intervention is effective in improving pain control in many opioid-tolerant patients without the need to increase their OME, thanks to advantage offered by opioid switching. Optimization of opioid use also explains the lack of resort of spinal analgesia, that was used in some cases in the previous study [7]. Thus, rather increasing the opioid doses, the outcome was achieved by individualization of the treatment, according to patients' characteristics and judicious use of opioids as well all the measures included in a comprehensive palliative care treatment. Also, the pattern of prescribed opioids changed. While transdermal fentanyl was confirmed to be the most common drug prescribed prior to admission, hydromorphone, which had been the most frequent drug prescribed at discharge in a previous study [7], has been withdrawn from the market some years ago in our country.

Almost all patients admitted to APCU did not have a BTP medication or were receiving just paracetamol or anti-inflammatory drugs. After admission intravenous morphine was more often given in combination with intravenous opioid dose titration process. As expected, to facilitate the discharge, intravenous morphine was progressively replaced by oral morphine and fentanyl preparations. Regretfully, BTP was poorly assessed or even untreated before

admission, despite this phenomenon has been the focus of literature with thousands of articles published in in the last 30 years, since the first definition was given [19]. Thus, there is an unmet need for educational issues in daily practice among physicians working in the oncologic setting.

The limitations of this study lie on the single-center study. The broader applicability in less specialized settings is unlikely, restricting the generalization of this data, also because of the variabilities still existing among APCUs in the world. This data should prompt further studies in APCUs, as well in other palliative care settings. Also, patients who died were excluded from analysis. This was justified by the awareness that typical symptom overexpression at end of life would have made the interpretation of the data unreliable. In any case, the number of these patients was really low.

CONCLUSIONS

In conclusion, an intensive and careful use of opioids allows to achieve an adequate analgesia in all patients examined in a short term and without increasing OME. This is one of the missions of an APCU, which is probably the best place to provide a comprehensive palliative care, of which uncontrolled pain is one of the multiple issues involving patient care.

Author Contributions. Sebastiano Mercadante: Conceptualization, methodology, original draft preparation, review and editing. Alessio Lo Cascio: Formal Analysis, editing. Giorgio Sapienza: Investigation, recruitment. Alessandra Casuccio: statistics, interpretation. All authors approved the final text.

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Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflict of Interest. Sebastiano Mercadante is an Editorial Board member of Pain & Therapy and was not involved in the selection of peer reviewers for the manuscript nor any of the subsequent editorial decisions. Giorgio Sapienza, Alessio Lo Cascio, and Alessandra Casuccio have nothing to disclose.

Ethical Approval. The protocol study was approved by the provincial ethical committee of Palermo. This study was performed in accordance with the Helsinki Declaration of 1964 and its later amendments. Patients' informed consent was obtained.

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