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The Use of High Doses of Oxycodone in an Acute Palliative Care Unit

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

Abstract

A retrospective study of patients who were prescribed controlled-release oxycodone (CRO) in a period of 3 years (2006-2008) was performed. A total of 212 patients were prescribed at discharge CRO for background analgesia; 129, 43, and 40 patients were prescribed doses of oxycodone of less than 120 mg/day (group L), 120 to 240 mg/day (group M), and more than 240 mg/day (group L), respectively. No differences in gender, primary diagnosis, and pain mechanisms were found, but doses were significantly lower in older patients ($P < .0005$). At discharge, adverse effects were mild and only a minority of patients were switched to other opioids. This study demonstrated that CRO administered in larger doses was safe and effective, showing versatility and flexibility similar to morphine.

Keywords

oxycodone, cancer pain, opioids, palliative care, supportive care, adverse effects

The analgesic ladder recommended by the WHO has been shown to provide efficient pain relief for a large number of cancer patients. Opioid administration is the primary therapeutic modality in the management of moderate-to-severe cancer pain. Morphine is considered the preferred drug because of its wide availability, varied formulations, and well-characterized pharmacologic properties.[1] Efficacious doses of morphine have a wide range, due to individual differences. Sometime morphine doses titrated individually to achieve adequate pain relief can require extremely high doses. Oral morphine has been shown to be a safe analgesic drug even in the high-dose range (more than 300 mg/day).[2-4]

Oxycodone was originally formulated in combination with nonopioids. Subsequently, oxycodone was shown to be as versatile and flexible as oral morphine in the management of cancer pain.[5] Controlled-release oxycodone (CRO) is widely accepted as an alternative to morphine, resulting as safe and effective as controlled-release morphine.[6] The use of relatively high doses of CRO (mean daily dose of about 230 mg) in terminal cancer patients was safe, efficient, and unrelated to shorter survival times.[7]

This article characterizes patients admitted to an acute pain relief and palliative care unit who received even larger doses of CRO for the management of cancer pain.

Patients and Methods

A retrospective study of a consecutive population of patients who were prescribed CRO during admission at an acute pain relief and palliative care unit in a period of 3 years (2006-2008) was performed. For each patient included in the study, demographic parameters, site of tumor, characteristics of pain, hospital stay, and doses of CRO prescribed at discharge were recorded.

Pain intensity was assessed by a numerical scale 0 to 10 and symptoms associated with opioid therapy or commonly present in patients with advanced cancer, such as nausea and vomiting, drowsiness, confusion, constipation, dry-mouth, and so on, using a scale from 0 to 3 (not at all, slight, a lot, awful), were recorded. Symptoms were assessed by the patient. Discress score (DS) was calculated from the sum of symptom intensity. During hospitalization, decisions regarding the administration of opioids and adjustment of dosage were based on assessment, patient's daily report, and rescue doses given during the preceding 24 hours. Patients are discharged home when pain doses are presumably stabilized and pain control has been achieved. The study sought to establish whether prescription of large doses of CRO was safe and effective. For this purpose, patients were divided in 3 groups: L (dose less of 120 mg/day),

[1] Pain Relief and Palliative Care Unit, La Maddalena Cancer Center, Palermo, Italy
[2] Palliative Medicine, Department of Anesthesia, and Intensive Care, 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

M (doses in the range of 120-240 mg 7 day), and L (doses higher than 240 mg/day).

Statistical Analysis

Data were analyzed by the Epi Info software (version 6.0, CDC, Atlanta, Georgia) and the SPSS Software 14.0 version (SPSS, Inc, Chicago, Illinois). Frequency analysis was performed with chi-square test. The one-way analysis of variance (ANOVA) was performed to evaluate difference in parametric variables. Moreover, to explore a relationship among doses of CRO and patients' characteristics, a series of logistic regression analyses were conducted. Independent variables included age, gender, and characteristics of pain. All P values were 2-sided and P values less than .05 were considered to indicate statistical significance.

Results

Of 1526 patients admitted in 3 years for pain and symptom control, 998 patients were discharged home with a strong opioid prescription. Globally, 234 patients were prescribed CRO during admission. Twenty-two patients were switched to the opioids, and 34 patients were switched to CRO. We collected 212 patients who were prescribed at discharge CRO for background analgesia (patients who initiated CRO and continued until discharge or who were switched to CRO). The mean age was 62.4 (13.2) years and 118 patients were males. Primary diagnoses were in a rank order: gastrointestinal (54), lung (52), urogenital (46), breast (27), others (33). Overall, the mean dose of oxycodone was 141 mg ($\pm$167, range 10-960 mg). In all, 129, 43, and 40 patients were prescribed doses of oxycodone of less than 120 mg/day (group L), 120 to 240 mg/day (group M), and more than 240 mg/day (group L), respectively. The mean doses in the 3 groups were 48.4 $\pm$ 25, 156.5 $\pm$ 30.5, and 435 $\pm$ 196, respectively. No differences in gender, primary diagnosis, and pain mechanisms were found ($P = .067$, $P = .43$, and $P = .783$, respectively). Doses were significantly lower in older patients ($P < .0005$). The mean admission time was 4.8 ($\pm$3.2) days. At hospital discharge, mean pain intensity was 2.9 ($\pm$1.9), adverse effects were mild in intensity (DS = 3.5 $\pm$ 1.7) and were not related to CRO doses ($P < 0.19$).

Discussion

Effectiveness and safety of high doses of opioids have been poorly reported in literature. In hospice and home care series of patients receiving oral morphine, 9% to 12% of patients required doses higher than 300 mg/day. Such relatively high doses did not influence the survival, attesting the safety of high doses of opioids in patients with advanced cancer who were responsive.[3,4] Similarly, doses in the range of 720 to 1100 mg of oral morphine were tolerated in very advanced cancer population.[2]

Oxycodone has been found to be as effective as morphine[6] and is the preferred drug for switching from morphine in United Kingdom.[8] Although recent data suggested that oxycodone is efficacious and well tolerated as a first-line opioid in doses of 20 to 40 mg/day after 3 weeks,[9] few reports have assessed patients receiving high doses of oxycodone. In an early experience, the mean highest doses of CRO were 160 mg after 12 weeks of treatment.[10] In a more recent study, the maximum mean dose was about 230 mg/day in patients with very advanced cancer with a mean survival of 12 days. High doses were unrelated to survival time.[7] Finally, in a mixed Italian population recruited in different settings, doses of CRO achieved after an average treatment duration of 37 days were 221 mg/day.[11]

In our experience, such doses are not considered particularly high, possibly due to the selection of patients admitted in our unit, who are already receiving opioids at relevant doses, and have a long-term survival. Most patients were receiving opioids and were titrated or switched to oxycodone to obtain the best balance between analgesia and adverse effects. According to existing studies reporting on high doses of CRO, we divided patients who were discharged home with a prescription of oxycodone in 3 groups, and considered high doses only those superior to the mean maximum doses administered in previous studies. According to department policy, patients are discharged home only on stable doses capable to maintain an acceptable pain relief (pain intensity of $\leq$4 on a numerical scale 0-10 and 2-3 doses of opioids as needed for breakthrough pain) and tolerable adverse effects. This study demonstrated that CRO administered in very high doses compared to those recorded in previous studies with the same purposes was safe and effective, showing versatility and flexibility similar to morphine, with doses titrated against intensity of pain.

As morphine, CRO showed a typical interindividual variability in doses. Although in an hospice experience age and gender did not influence the CRO dose,[7] in this study, older patients received doses significantly lower in older patients. The difference may be related to the different population examined. Of interest, most of the patients examined were still on oncologic treatment and had a prolonged survival, differently from patients with a very short survival typically observed in hospice patients.[7] Survival, although presumably longer, was not addressed, and patients who died in the unit were not accounted for the study. The lower doses of CRO found in older population reflect similar observation reported with other opioids[12] and are likely to be related to well-known pharmacokinetics of opioids in aged population.[13,14] Pain mechanisms did not influence CRO doses, remarking the potential efficacy of oxycodone in the different types of pain, including neuropathic pain.[15] Given the retrospective nature of this study, adjuvants were freely administered. However, the consumption of adjuvants was not different from that reported with other opioids. The role of CRO in patients with neuropatic pain should be better addressed in appropriate study with specific designs and is beyond the aim of the current study.

Adverse effects were rarely dose-limiting, and safety was witnessed at time of discharge, which, as per protocol, required the achievement of an acceptable balance between analgesia

and adverse effects. Patients were discharged with an acceptable DS, which has been used to globally monitor the intensity of opioid-related symptoms.[16] It is expected, however, that after starting titration with CRO, 15% of patients may discontinue the drug for adverse effects.[9,10] In this study, only a minority of patients were switched to other opioids during admission (9.4%). The principal limits of this survey is the retrospective analysis, which, however, has a little influence on the results reported, according to which high doses of CRO, over 240 mg/day, are safe and effective.

Declaration of Conflicting Interests

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