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Pharmacological approach to chronic visceral pain. Focus on oxycodone controlled release: an open multicentric study

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Abstract. – *Background and Objectives:* **Visceral pain is a significant issue for patients, and the importance of treating pain is underestimated. New opioid formulations, the primary treatment option for moderate-to-severe pain, have been shown to be effective, but no studies have been conducted to address the efficacy of these agents for visceral pain. This study was conducted to determine the incidence of visceral pain in patients with uncontrolled moderate-to-severe pain, and to evaluate the efficacy of controlled-release (CR) oxycodone in this context.**

Materials and Methods: **In this multicenter, prospective, observational study, 967 of 980 evaluated patients were included, 350 (36.2%) of whom presented mainly visceral pain. In most cases (57.0%), patients had experienced pain for ≤3 months, and the majority (94.9%) were cancer patients. Pain was uncontrolled in 340 (97.1%) patients, and was rated as severe in >2/3 of patients (mean numerical rating scale (NRS) value 7.04 ± 1.68). Patients with uncontrolled pain were given oxycodone CR; all completed the 15-day study and no patient was switched to an alternative opioid.**

Results: **Oxycodone CR was associated with significant reductions in mean NRS value at day 3, 7 and 15 (final mean NRS 2.37 ± 1.59) and the proportion of patients experiencing severe pain had decreased by the end of the study to 1.5%. The SF-12 questionnaire showed significant improvements in quality of life in all domains, and oxycodone CR was well tolerated.**

Conclusions: **Oxycodone CR appears to be a very well tolerated and effective treatment for patients with visceral pain.**

Key Words:
Cancer Pain, Oxycodone, Visceral pain, Non-cancer pain.

Introduction

Visceral pain is a result of damage to the organs innervated by the sympathetic nervous system[1]. Accurate localization of visceral pain is difficult, since the nerve fibres innervating these organs cannot precisely transmit pain stimuli to the central nervous system; few studies have been conducted to address optimal treatment strategies for visceral pain, therefore such strategies are still to be defined[2].

The control of visceral pain is a central issue for a number of different pathological conditions, particularly in oncologic diseases[3]. Notably, the importance of pain treatment in cancer patients is still underestimated; the Guidelines of the European Society of Medical Oncology (ESMO) emphasized the importance of controlling all components of pain, including visceral pain, in cancer patients using different pharmacological therapies following the so-called "pain ladder" described by the World Health Organization (WHO)[4]. At the first step of the ladder, corresponding to mild pain, non-steroidal anti-inflammatory drugs (NSAIDs) are recommended, despite this class of drugs being associated with gastrointestinal and renal toxicity[4]. As pain progresses to moderate or severe intensity, different strategies are advocated[4]. In recent years, opioids, administered in new formulations, have shown efficacy in this therapeutic context and are now recommended for the treatment of moderate-to-severe cancer pain[4]. These new formulations include controlled-release (CR) codeine, dihydrocodeine, oxycodone, morphine and tramadol. Morphine is considered

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the standard treatment for chronic moderate-to-severe cancer pain[4]. However, recent findings have suggested additional clinical benefit of oxycodone CR, compared with morphine[5-11]. Similar results were obtained for non-cancer visceral pain[12,13]. Oxycodone is a strong opioid interacting with mu- and kappa-opioid receptors, with a characteristic pharmacological profile[14]. In the CR formulation, oxycodone presents a biphasic absorption pattern, i.e. an initial rapid increase in concentration followed by a prolonged phase, offering some advantages in dosing schedule compared with other formulations, such as immediate-release oxycodone[10].

However, while the efficacy of oxycodone CR in the treatment of cancer and non-cancer pain has been established, no specific studies have been conducted to address the effectiveness of this drug in patients with visceral pain. The aim of this multicentric study, conducted in an Italian setting in patients with uncontrolled moderate-to-severe pain of various aetiology, was to determine the incidence of the visceral component of pain, and to evaluate the efficacy of oxycodone in this therapeutic context.

Patients and Methods

Study Setting and Design

This was a multicenter, prospective, observational trial conducted in Italy in 4 hospital centres specializing in pain treatment. The study started in June 2008 and ended in December 2008. The trial was coordinated by Professor S. Liguori, Pain Therapy Department, Bergamo, Italy. The Ethical Committees of each centre approved the study design and all patients provided written informed consent prior to trial enrolment. The investigation was conducted according to the declaration of Helsinki guidelines (revised 2005 version).

Consecutive patients were included in the study if they met the following inclusion criteria: (1) age ≥18 years; (2) pain uncontrolled [score ≥4 on a 10-point numerical rating scale (NRS), where 0=no pain and 10=worst possible pain] with therapy administered at the time of inclusion. Exclusion from the trial was based on the following criteria: (1) patients intolerant to oxycodone; (2) patients with severe renal insufficiency (serum creatinine level >3 mg/dL) or moderate-to-severe liver insufficiency; (3) patients unable to take oral medications; (4) pregnant or breast-feeding women. Included patients were evaluated at baseline by a trained physician, who assessed the main component of pain (somatic, neuropathic, visceral, or mixed). Patients with visceral pain stopped their previous pain therapy and started treatment with daily oxycodone CR (OxyContin™; Mundipharma Pharmaceuticals, as 5, 10, 20, 40 or 80 mg tablets)* for 15 days. The switch to oxycodone CR was performed gradually according to international guidelines; the initial oxycodone CR dose was individualized for each patient in accordance with standard conversion tables, taking into consideration the patient's pharmacological history. Oxycodone CR treatment was then titrated over a total period of 7 days. If the patient did not respond to oxycodone CR (reduction <50% in the NRS score compared with baseline) after 7 days with an appropriate titration scheme, or experienced severe adverse effects, treatment with oxycodone CR was interrupted; the patient was then switched to an alternative opioid (morphine or fentanyl) and discontinued from the study. Use of morphine sulphate as a rescue medication during oxycodone treatment was permitted.

Measurements

At baseline, pain evaluation was undertaken by a trained physician and included the following: cause of pain; duration of pain prior to study; history of prescribed pain treatment; and pain intensity according to NRS score. Patients were also asked to judge their previous pain treatment, if any, as "highly effective" "effective" "poorly effective" or "not effective". Patients underwent further clinical examination, conducted by the same physician, after 3, 7 (titration visits) and 15 days of treatment with oxycodone CR.

The primary efficacy endpoint was the NRS score at each time point compared with the previous time point. Other assessments included evaluation of quality of life via the short form (SF)-12 questionnaire, administered by the same physician, and the incidence and severity (mild, moderate, severe) of adverse events, measured using a written questionnaire completed by the patient. At the end of the study period, patients judged oxycodone treatment as "highly effective" "effective" "poorly effective" or "not effective".

*The use of trade names is for product identification purposes only and does not imply endorsement.

Statistical Analysis

Data were means ± SD. The comparison between consecutive time points was performed using the Student's t test. A p value <0.05 was considered as statistically significant.

Results

Patient Characteristics

In total, 980 patients were evaluated for inclusion in the study (Figure 1), 13 of whom were not suitable for inclusion. Baseline characteristics of the 967 patients included in the study are summarized in Table I. The largest pain subset of the 967 patients included in the study were those affected by pain with mixed (somatic + visceral) components; 350 (36.2%) subjects presented mainly visceral pain. In most cases (57.0%), these patients had experienced pain for ≤3months prior to study initiation. The large majority of included patients (94.9%) were cancer patients. The most frequent cancer was colon carcinoma (21%), followed by pancreatic carcinoma (14%) and gastric carcinoma (10%).

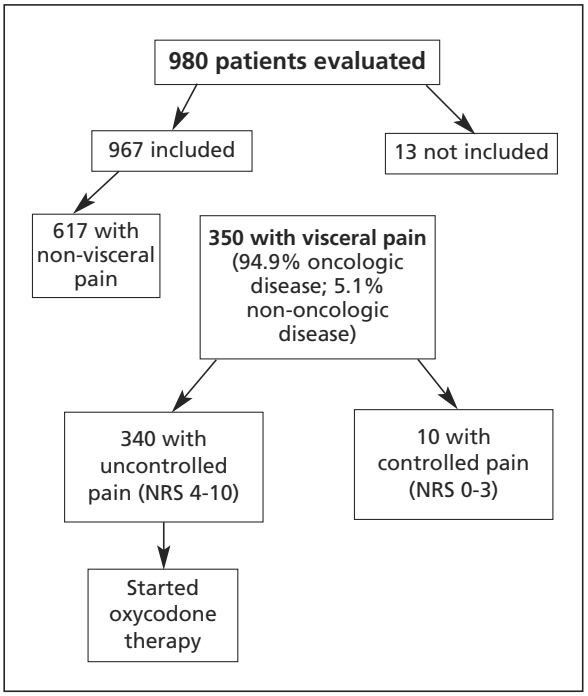

Figure 1. Patients' disposition throughout the study. NRS: numerical rating scale.

Table I. Baseline characteristics of included patients.

Total number of patients	967
Main pain component, number (%)	
Somatic	153 (15.8)
Visceral	350 (36.2)
Neuropathic	70 (7.2)
Mixed	393 (40.64)
Patients with visceral pain	
Males, number (%)	187 (53.5)
Age, years	
Range	25-100
Mean±SD	64.1 ± 13.1
Pain duration, number (%)	
0-3 months	200 (57.0)
4-6 months	101 (29.1)
> 6 months	46 (13.1)
Not available	4 (1.1)
Disease	
Oncologic	332 (94.9)
Non-oncologic	18 (5.1)

Baseline Pain Evaluation and Previous Therapy

Pain was uncontrolled in 340 (97.1%) patients with visceral pain, and in more than 2/3 of patients was rated as severe (NRS 7-10); the mean NRS value was 7.04 ± 1.68. Before entering the study, most patients (40.6%) were on weak opioid therapy, mainly with tramadol (Table II). A lower percentage of patients was on strong opioids or NSAIDs (Table II). In 65.5% of patients, strong opioids were administered transdermally and in 34.5% of cases they were administered orally (Table II).

The majority of patients (90.8%) judged previous therapy as "poorly effective" or "not effective", with 8.62% judging previous therapy as "effective" and 0.58% as "highly effective".

Oxycodone CR Treatment

The 340 patients with uncontrolled pain were given oxycodone CR treatment; all patients completed the study period of 15 days and no patient was switched to an alternative opioid treatment. At baseline, mean oxycodone CR dose was 35.5 mg/day; this dosage was then gradually titrated to 45.0 mg/day (day 3) and 50.5 mg/day (day 7). The dosage remained constant until the end of the study (mean dose 50.1 mg/day; Figure 2).

Oxycodone treatment was associated with a significant reduction in the mean NRS throughout the study period (day 3 $p<0.00001$ vs base-

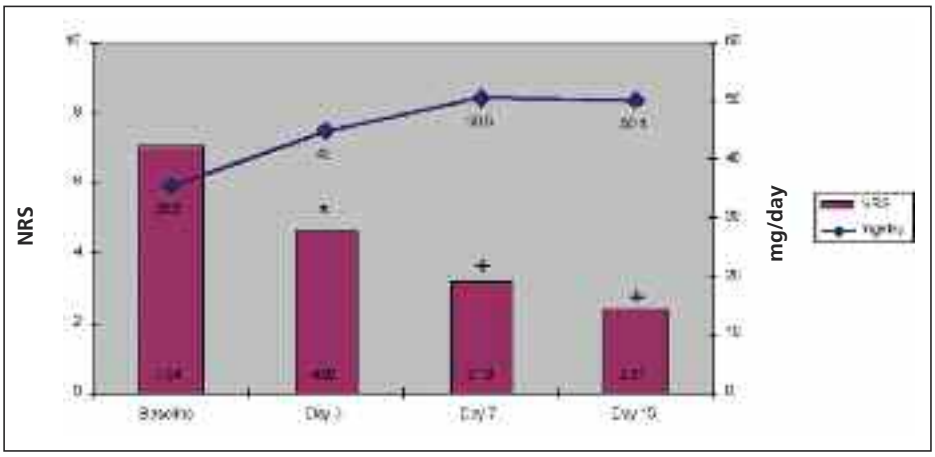

Figure 2. Qualitative correlation between NRS score and oxycodone dose during the study period. (*p <0.00001 vs baseline; + p <0.0003 vs baseline. NRS: numerical rating scale.

line; day 7 p<0.0003 vs baseline; day 15 p<0.0003 vs baseline; Figure 2). The final mean NRS value was 2.37±1.59. The proportion of patients experiencing severe pain decreased during the study period, while the percentage of subjects with mild pain increased accordingly (Figure 3). At study end, the proportion of patients experiencing severe pain was 1.5%.

The evaluation of quality of life via the SF-12 questionnaire at the end of the study indicated an improvement in all domains (Figure 4). In total, 91.94% of patients judged oxycodone treatment to be "highly effective" or "effective". Only 6.87% of patients judged oxycodone CR therapy to be "poorly effective" and only 1.19% as "not effective".

Oxycodone treatment was well tolerated; no serious adverse events were reported and most adverse events were of mild intensity (Table III).

Discussion

This study evaluated, for the first time, the use of oxycodone for the treatment of visceral pain in a specific population of patients with cancer and non-cancer pain. Visceral pain accounts for a large proportion of the pain experienced in both cancer patients and those with a variety of other illnesses, as demonstrated by the present research. However, pain, and the importance of effectively treating such pain, remains largely underestimated[4]. Moreover, currently utilized strategies for the treatment of this component of pain require further investigation, as there is no standard optimized therapeutic regimen specifically for the treatment of visceral pain[2].

Opioids have been shown to be efficacious in the treatment of pain[4,15]. Notably, the use of mu-

Table II. Pain medications administered before study entrance.

	% (Number) of patients (n = 322)
NSAIDs (Paracetamol, ketorolac, diclofenac, nimesulide, ibuprofen)	25.4% (n = 82)
Others (Antiepilectic, Anxiolytic, Anticolinergic, Antispastic)	1.5% (n = 5)
Weak opioids	
Tramadol	32% (n = 103)
Codeine	10.9% (n = 35)
Strong opioids	
Transdermal opioids	
Buprenorphine	3.6% (n = 12)
Fentanyl	15.5% (n = 47)
Oral opioids	
Oxycodone	5.7% (n = 19)
Morphine	4.3% (n = 15)
Hydromorphine	1.1% (n = 4)

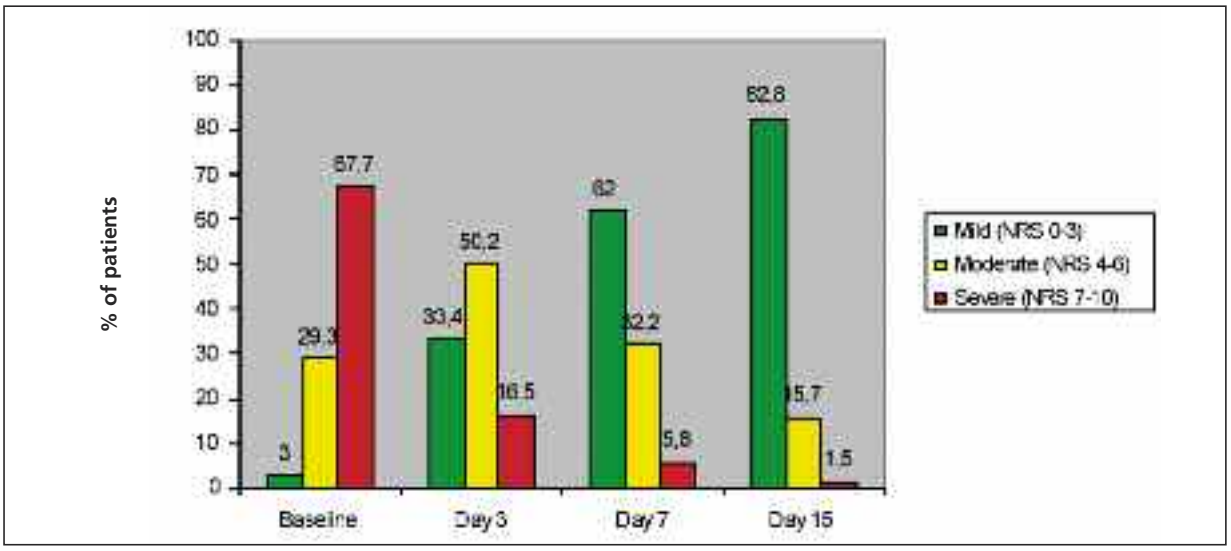

Figure 3. Proportion of patients experiencing mild (NRS score 0-3), moderate (NRS score 4-6) or severe pain (NRS score 7-10) at each study timepoint. NRS: numerical rating scale.

agonist opioids, such as morphine, is associated with lower efficacy than kappa agonists. In accordance with this finding, oxycodone has emerged as an effective alternative to morphine, as it is characterized by an high affinity towards both mu and kappa receptors[7,14,16-19].

The results of the present study, conducted in the very specific context of patients with visceral pain, show that oxycodone CR provides fast and effective relief from pain, as well as marked improvements in quality of life, with a limited inci-

Table III. Adverse events reported in the study period (% of patients).

Day 15	Mild intensity	Moderate intensity	Severe intensity
Nausea	34	11	1
Vomiting	12	4	1
Sleepiness	23	18	2
Constipation	48	27	5
Dry mouth	19	6	0
Itching	5	2	0
Other	3	0	0

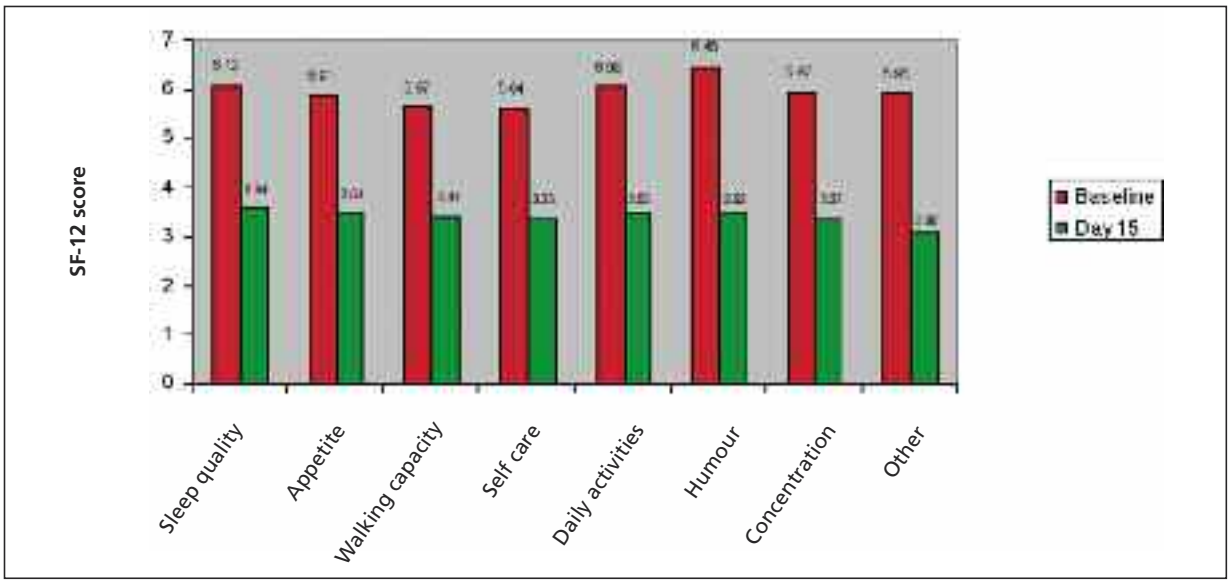

Figure 4. Scores of the different domains of the Short Form-12 Questionnaire at baseline and at study end.

dence of adverse events. Of note, these findings were obtained in patients with pain uncontrolled with other therapies.

These results are in good agreement with previous studies investigating the use of oxycodone CR in the treatment of pain associated with cancer as well as that associated with non-oncologic causes[5-13]. However, this investigation was an observational non-comparative study and therefore the limitations associated with such a trial design should be taken into account when interpreting the results.

In conclusion, this study suggests that the visceral component of pain, which is a widespread condition both in cancer and non-cancer patients, and is often difficult to treat, can be effectively controlled with oxycodone CR, with an important improvement in quality of life.

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