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Morphine Versus Oxycodone in Pancreatic Cancer Pain
A Randomized Controlled Study

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Objective: According to experimental findings, oxycodone (OX) could have some advantages over morphine (MO) in clinical models of visceral pain. It was hypothesized that OX could have some advantages over MO in terms of efficacy and dose escalation in pancreatic cancer pain.

Methods: Sixty patients with pancreatic cancer with a pain intensity rating of 4/10 who required opioids were included in the study. Patients were randomized to receive 30 mg/d of sustained release oral MO or sustained release oral OX (20 mg/d). Opioid doses were increased according to the clinical needs. Daily doses of opioids, pain and symptom intensity were recorded at admission (T0) and at weekly intervals for the subsequent 4 weeks (T1, T2, T3, and T4), with an extension at 8 weeks (T8). Opioid escalation index (OEI) as percentage (OEI %) and in mg (OEI mg) was calculated.

Results: Nineteen and 20 patients in groups OX and MO, respectively, were followed for the entire period of study (T4). No differences between groups were found in age ($P = 0.400$), Karnofsky ($P = 0.667$), or escalation indexes at T4 and T8 (OEImg, $P = 0.945$ and OEI %, $P = 0.295$). No statistical differences in pain and symptoms intensity between the groups were observed.

Conclusion: OX and MO provided similar analgesia and adverse effects with similar escalating doses in patients with pancreatic cancer pain, resembling observations reported in the general cancer pain population. The experimental hypothesis that OX would be superior to MO in the clinical model of pancreatic cancer pain was not confirmed.

Key Words: pancreatic cancer pain, opioids, oxycodone, morphine, visceral pain

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Oral morphine (MO) has been widely used for treating cancer pain of moderate-to-severe intensity, and remains the opioid of choice for its familiarity, availability, and costs rather than proven superiority.[1] Oxycodone (OX) has been used clinically for the same indications and has been found to provide analgesia comparable with that of MO and mediated primarily in the central nervous system.[2] However, experimental observations suggest that OX and MO produce antinociception through distinctly different opioid receptor populations and OX seems to act as κ-agonist with a relatively low affinity for μ-opioid receptors.[3] The κ-agonists exert analgesic activity in a wide variety of visceral pain models. These effects are mediated at peripherally located κ-receptors and possibly through additional nonopioid action at sodium channels located on peripheral nerve endings. Their analgesic potency seems to be enhanced in the presence of local inflammation.[4] The profile of κ-agonists in visceral pain models suggests that opioids with these characteristics might be useful to treat a variety of visceral pain conditions.

Although MO and OX have been used for years, directly comparing their pharmacology and effects has been studied more intensively over the last decade. Controversies exist about the intrinsic antinociceptive effects of OX.[3,5–11] Experimental and human studies suggest that these effects are distinctly different from those mediating effects of MO,[3,5,6] which could explain the asymmetric tolerance with MO.[7] In a multimodal, tissue-differentiated experimental pain models in humans, OX showed a superior analgesic effect to MO in visceral pain, but a similar analgesia in pain modulation of the skin and muscles.[8] This differentiated effect has been attributed to the peripheral κ-agonist activity of OX.[6] OX plasma concentration correlated better with the course of the analgesia with no delay in the visceral pain measures, in comparison with MO.[9] However, other experiments have shown that the effects of OX are likely mediated through μ-opioid receptors.[10] More recently, OX has been reported to exhibit a generalized effect, elevating threshold for different kinds of stimulation, including cutaneous, deep somatic, and visceral pain stimulation.[11]

A cancer pain syndrome with an important visceral component, because of a prevalent local spread, at least initially, is associated with pancreatic cancer. A neurolytic celiac plexus block has been advocated to treat the visceral component in advanced cancer patients.[12] Given these experimental findings and the potential properties of OX, we hypothesized that OX could have some advantages over MO in terms of efficacy and dose escalation in pancreatic cancer pain.

PATIENTS AND METHODS

Sixty patients with pancreatic cancer who required opioids were included in the study. Inclusion criteria were pancreatic cancer with a local disease, presenting abdominal pain with an intensity of 4/10 or more in a numerical rating scale of 0 to 10, and no longer responsive to nonopioid analgesics. Exclusion criteria were distant and bone metastases, or prevalent somatic pain because of evident peritoneal involvement, changes in chemotherapy

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regimen, radiotherapy, hepatic or renal failure, cognitive failure, lack of cooperation, extreme ages (below 18 and above 80 y), and a Karnofsky status less than 50. Informed consent and institutional approval were obtained.

Patients were randomized by a computer system in 2 groups. Patients in group MO started with 30 mg/d of sustained release oral MO, whereas patients in group OX received equivalent MO doses of sustained release oral OX (20 mg/d), according to an approximate MO-OX ratio of 1.5:1.[13,14]

For patients who required an increase in the dose because of increasing pain (more than 4/10, or more than 3 breakthrough pain medications per day) during the period of study, opioid doses were increased according to the clinical needs. In both groups, oral MO in doses of 1/6 of the daily dose was provided as a rescue dose for episodes of breakthrough pain (5 mg of oral MO, initially).

Patients were recruited and followed during admission to the palliative care unit, as outpatients and at home. Physicians provided frequent call contacts to adjust the opioid dose at any time and to reproduce a realistic clinical-care scenario. Adjuvants and symptomatic drugs were prescribed as indicated by the clinical situation. The following parameters were collected as reported by patients: average pain intensity in the last 24 hours (numerical rating scale 0 to 10), opioid-related symptoms, including nausea and vomiting, drowsiness, and confusion, by using a scale from 0 to 3 (absent, slight, moderate, and severe). For constipation the scale was: 0 = one passage/1 to 2 days, 1 = one passage/3 to 4 days, 2 = one passage/more than 4 days, and 3 = only by enema. Daily doses of opioids, pain and symptom intensity were recorded at admission (T0) and at weekly intervals for the subsequent 4 weeks (T1, T2, T3, and T4), with an extension at 8 weeks (T8). Opioid escalation index (OEI) as percentage (OEI %) was calculated according to the following formula: OEI %: $[(x-y)/1]/d \times 100$, where x is dose at the end of study and y is the dose at admission. OEI mg was calculated with the following formula: $(x-y)/d$.[15] The number of patients who needed an opioid switching, because of an inconvenient balance between analgesia and adverse effects, or unavailability of oral route, were recorded.

Statistics

The primary objective of the study was to evaluate pain intensity scores at different time intervals. A power analysis indicate that a sample size of 25 patients per group would allow the detection of a 20% difference in pain intensity score ($P < 0.05$, power = 0.8). This computation assumes that the mean difference is 0.20 with a 95% confidence interval of 0.07-0.33 and the common within-group SD of 0.28. Frequency analysis was performed with χ^2 test. The univariate repeated measures analysis of variance and the paired Wilcoxon signed rank test were used to compare the means or the scores of parametric or nonparametric variables, respectively, at the different time intervals. The 1-way analysis of variance and Mann-Whitney *U* statistic test was used to compare the different parametric or nonparametric variables. All *P* values were 2-sided and values less than 0.05 were considered statistically significant.

RESULTS

Forty-six patients of 60 randomized patients completed baseline evaluation (T0), 21 patients in group OX and 25 in group MO. The remaining 14 patients did not complete baseline evaluation because they were lost to follow-up. Of the forty-six patients, 27 patients were females, the mean age was 63.2 years (SD 9.48), and the mean Karnofsky status was 70 (SD 11.8).

Nineteen and 20 patients in group OX and MO, respectively, completed 4 weeks of follow-up (T4). In group OX, 1 patient died before T2, two patients were switched to transdermal fentanyl, and 3 patients were switched to intravenous MO for bowel obstruction. Eight patients died before T8 (see flow diagram in Table 1, and the number of patients evaluated at the different intervals in Table 2).

In group MO, 1 patient was switched to transdermal buprenorphine for bowel obstruction and died before T1, one patient died before T3, three patients were switched to intravenous MO for bowel obstruction, and 2 patients were switched to intravenous MO between T4 and T8. Eight patients died before T8 (see flow diagram in Table 1, and the number of patients evaluated at the different intervals in Table 2). The number of patients who died before T8 was similar in the 2 groups, and patients who were switched to other opioids.

No differences were found between groups in age ($P = 0.400$), Karnofsky ($P = 0.667$), and escalation indexes (OEI mg, $P = 0.945$ and OEI %, $P = 0.295$), when comparing T4 to T8. Data on pain and symptom intensity, opioid doses, and OEI of OX and MO are reported in Table 2. No statistical differences were observed. The number of rescue doses was small and similar between the 2 groups. No differences in the number of patients receiving adjuvant or symptomatic drugs were found between the 2 groups.

DISCUSSION

Recent investigations have shown that opioids may have distinct profiles under various experimental conditions.

TABLE 1. Flow Diagram of Randomized Patients

30 Patients Randomized on Oxycodone		30 Patients Randomized on Morphine
46 patients with a baseline evaluation at T0		
21 patients	T0	25 patients
9 patients lost in follow-up		5 patients lost in follow-up
1 patient died		1 patient switched and died
1 patient switched		1 patient died
		3 patients switched
19 patients completed	T4	20 patients completed
4 patients switched		2 patients switched
8 patients died		8 patients died
7 patients	T8	10 patients

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TABLE 2. Pain, Symptom Intensity, and Opioid Doses in Groups Treated With OX and MO Before Starting Opioids (T0), at Weekly Intervals (T1, T2, T3, and T4), and After 8 Weeks

	T0	T1	T2	T3	T4	T8
No. patients						
OX	21	21	20	19	19	7
MO	25	24	24	23	20	10
Pain						
OX	7.19 (0.9)	2.09 (2.07)*	1.8 (1.76)*	2.79 (2.04)*	3.15 (3.0)*	2.0 (1.2)*
MO	7.24 (0.66)	1.41 (1.81)*	1.62 (2.04)*	2.17 (2.14)*	2.35 (2.36)*	1.2 (1.03)*
P	0.896	0.232	0.528	0.297	0.492	0.189
Nausea						
OX	0.24 (0.43)	0.38 (0.50)	0.50 (0.60)*	0.58 (0.77)*	0.84 (0.90)*	0.85 (0.70)*
MO	0.48 (0.65)	0.54 (0.78)	0.54 (0.66)	0.56 (0.66)	0.60 (0.75)	0.40 (0.70)
P	0.201	0.700	0.883	0.910	0.400	0.143
Drowsiness						
OX	0.20 (0.41)	0.45 (0.60)	0.47 (0.61)	0.37 (0.60)	0.37 (0.60)	0.28 (0.50)
MO	0.36 (0.60)	0.83 (0.76)*	0.58 (0.58)	0.43 (0.60)	0.35 (0.59)	0.50 (0.70)
P	0.342	0.086	0.489	0.652	0.917	0.561
Confusion						
OX	0.15 (0.37)	0.25 (0.55)	0.26 (0.56)	0.16 (0.37)	0.37 (0.49)*	0.71 (0.49)*
MO	0.16 (0.37)	0.29 (0.55)	0.25 (0.44)	0.26 (0.45)	0.25 (0.44)	0.10 (0.31)
P	0.928	0.722	0.842	0.424	0.429	0.011*
Dry mouth						
OX	0.15 (0.36)	0.45 (0.60)*	0.31 (0.47)	0.36 (0.59)*	0.63 (0.68)*	0.71 (0.48)*
MO	0.32 (0.55)	0.75 (0.60)*	0.62 (0.64)*	0.65 (0.64)*	0.60 (0.68)*	1.10 (0.87)*
P	0.282	0.091	0.108	0.122	0.876	0.318
Constipation						
OX	0.40 (0.60)	0.55 (0.68)	0.36 (0.49)	0.36 (0.49)	0.63 (0.68)	0.57 (0.53)
MO	0.72 (0.79)	0.79 (0.88)	0.75 (1.11)	0.87 (1.05)	0.70 (0.92)	0.80 (0.91)
P	0.171	0.401	0.261	0.108	0.926	0.741
Opioid doses						
OX	20	23.8 (7)	25.5 (8)	27.9 (9)	33.1 (14)*,**,***	45.7 (24)*,**,***,†
MO	30	35.0 (9)*	36.2 (14)*	41.0 (19)*,**	42.6 (21)*,**	60.0 (46)*,**
OXEI mg					0.44 (0.47)	0.30 (0.33)
OXEI %					2.19 (2.33)	1.50 (1.64)
MOEI mg					0.42 (0.70)	0.29 (0.52)
MOEI %					1.40 (2.34)	0.97 (1.75)

Data are expressed as mean (SD).
*$P < 0.05$ versus T1.
**$P < 0.05$ versus T2.
***$P < 0.05$ versus T3.
†$P < 0.05$ versus T4.
MO indicates morphine; MOEI, opioid escalation index of MO; OX, oxycodone; OXEI, opioid escalation index of OX.

Specifically marked differences in the antinociceptive profiles of OX and MO have been found in some experimental and clinical models, including chronic pancreatitis and thermal pain threshold in the esophagus, suggesting significant between-opioid differences in opioid receptor signaling.[6,16] The κ-opioid receptor agonists are particularly effective analgesics in experimental models of visceral pain, acting peripherally.[4,17,18] It has been shown that OX may be superior to MO in the treatment of visceral pain,[6,8] possibly because of the prevalent peripheral activity of OX as a putative κ-agonist,[3] and a relatively low affinity for μ-receptors.[19,20] We selected patients with pancreatic pain as a model of clinical visceral pain for its tendency to maintain a local spread, although pain mechanism may change in time because of the progression of disease.[21] According to these observations, it was expected that OX would have offer some advantages over MO in terms of analgesia and opioid doses, because of its κ-agonist activity with preferential localization in visceral tissues.

This study showed no differences between OX and MO started at equivalent doses in patients with pain associated with pancreatic cancer. Pain intensity similarly decreased in both groups and the trend in symptom intensity was similar, as well as the use of breakthrough pain medication. MO was used in both groups as no immediate release preparation of OX was available, unless in combination.

In group OX, it was noted a tendency to an increase in intensity of nausea after 2 weeks, and confusion after 8 weeks, although differences did not attain statistical significance in comparison with group MO at the different intervals examined. Considering the concomitant abdominal disease and treatments received, and possibly the low number of patients, it is unlikely to draw conclusion about the responsibility of an opioid as a causal factor in this context.

The findings of this study could be attributed to different factors. First, experimental conditions are often different from a clinical scenario and experimental findings can not always be translated in daily practice.[21] In cancer patients, multiple mechanisms play a role, including, for example, the inflammatory factors or apparent sprounting and then destruction of sensory and sympathetic fibers that innervate the pancreas, which are able to mask pain in the

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early stage of disease.[22] Secondly, pancreatic pain has been regarded either as a neuropathic pain condition, because of the diffuse infiltration of nerves and celiac plexus, or somatic pain syndrome, because of the involvement of peritoneum. As a consequence, the possible advantages observed in experimental conditions of visceral pain may be masked by all the factors playing a role in a cancer patient. Third, OX and its metabolites may still have sufficient μ-receptor activity,[23] and an aggressive local disease, like cancer, may impair the expression of peripheral κ-opioid receptors.

Weaknesses of this study include the relatively small size of the sample. As expected in a population with pancreatic cancer with a late diagnosis, many patients did not have complete data for different reasons, commonly reported in advanced cancer population.[24] The sample power dropped at 65% at the end of study (4 wk), limiting the statistical validity. The absence of some differences does not constitute a claim for equivalence, because of the inevitable number of dropouts. However, the dropout rates reported in this study was similar in both groups, consistent with that observed in earlier comparative studies of opioids[13,21] and reflects the difficulties in performing controlled trials in this population.[24] The choice of not blinding the study was directed by the need to reproduce a daily clinical scenario allowing the therapeutic flexibility needed to reproduce what happens in the daily activity. Studies with drugs used for relatively prolonged periods of time are very difficult to perform, particularly if patients are then followed up by phone interviews and visits at the outpatient clinic, and it is difficult to maintain blinding. Finally, a certain number of patients developed bowel obstruction, which is typical complication of pancreatic cancer, and could not continue to take the study drugs orally.

In conclusion, OX and MO provided similar analgesia and adverse effects with similar escalating doses in patients with pancreatic cancer pain, resembling observations reported in the general cancer pain population.[2] The experimental hypothesis that OX would be superior to MO in the clinical model of pancreatic cancer pain was not confirmed.

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