Morphine or Oxycodone in Cancer Pain?

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Oxycodone is an opioid analgesic that closely resembles morphine. Oxymorphone, the active metabolite of oxycodone, is formed in a reaction catalyzed by CYP2D6, which is under polymorphic genetic control. The role of oxymorphone in the analgesic effect of oxycodone is not yet clear. In this study, controlled-release (CR) oxycodone and morphine were examined in cancer pain. CR oxycodone and morphine were administered to 45 adult patients with stable pain for 3–6 days after open-label titration in a randomized, double-blind, cross-over trial. Twenty patients were evaluable. Both opioids provided adequate analgesia. The variation in plasma morphine concentrations was higher than that of oxycodone, consistent with the lower bioavailability of morphine. Liver dysfunction affected selectively either oxycodone or morphine metabolism. Three patients with markedly aberrant plasma opioid concentrations are presented. Significant individual variation in morphine and oxycodone metabolism may account for abnormal responses during treatment of chronic cancer pain.

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Oral opioids are the treatment of choice for chronic cancer pain (1). A change of opioid is recommended if pain relief with one opioid is inadequate or unacceptable adverse effects occur (2). Cross-tolerance between different mu opioid receptor agonists is incomplete (3) and equianalgesic doses may vary depending on the sequence of opioid administration (4).

Oxycodone is a semisynthetic opioid with a pharmacodynamic profile closely resembling that of morphine. Clinical studies have shown that oxycodone provides efficient pain relief in acute postoperative pain (5) and in chronic pain (6). Oxymorphone, an active metabolite of oxycodone, is formed in the liver in an O-demethylation reaction, mediated by the enzyme CYP2D6 (7). CYP2D6 is under polymorphic genetic control and is absent in 5–10% of the Caucasian population (poor metabolizers, PM) (8). The role of oxymorphone in the analgesic effects of oral oxycodone is unclear.

The aims of this study were to examine the pharmacokinetic differences between oxycodone and morphine in a stable situation in patients with chronic cancer pain and to determine the common factors causing clinically significant pharmacokinetic alterations. The CYP2D6 phenotype was determined in order to support the conclusions.

The pharmacodynamic results of this study have been presented in greater detail in a separate article (4).

MATERIAL AND METHODS

Forty-five adult patients presenting with chronic, stable cancer pain requiring opioid analgesics participated in the study. The patients had to be cooperative and able to take oral medication. Written informed consent was obtained from each participant and the study was approved by the institutional Ethics Committee and the National Agency for Medicines of Finland. The characteristics of the 27 patients who completed the study are presented in Table 1.

Drugs

The study design was a randomized, double-blind, cross-over comparison of CR oxycodone and CR morphine. Computer-generated randomization was used. CR oxycodone 20 mg tablets (The Purdue Frederick Company, Norwalk, Connecticut), CR morphine 30 mg tablets (MS Contin, Napp Laboratories, Cambridge), matched placebo tablets and respective escape analgesic solutions (oxycodone hydrochloride, 2.7 mg/ml and morphine hydrochloride, 4.0 mg/ml), were provided by the hospital pharmacy.

Study protocol

The patients were randomized to receive either CR oxycodone or CR morphine in an open-label titration phase, for a maximum of 21 days. The initial total daily opioid dose was calculated based upon the past three days of

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opioid analgesic therapy using standard conversion charts (1). The respective opioid solution was administered as escape analgesic medication in a dose of approximately 1/6 to 1/8 of the daily dose of CR oxycodone or CR morphine.

Dose titration was continued until effective pain relief (pain intensity none or slight and escape analgesic doses ≤ 2 per day) with acceptable adverse effects was achieved for at least 48 h. Daily contact with the patient was maintained during the open titration and the double-blind phases of the study. In their diaries the patients recorded each dose of scheduled and escape study medication, concomitant medications, intercurrent illnesses and adverse experiences. In addition, the patients assessed their pain intensity four times each day on a 4-point verbal rating scale (0 = none, 1 = slight, 2 = moderate, 3 = severe) and the acceptability of therapy twice daily on a 5-point verbal rating scale (0 = very poor, 1 = poor, 2 = moderate, 3 = good, 4 = excellent).

When the total daily opioid dose had been stable for at least 48 h without unacceptable adverse effects, the patient was re-randomized to a double-blind cross-over sequence. The daily dose of CR oxycodone or CR morphine was known from the last day of the titration phase or calculated by the pharmacist using a ratio of oxycodone : morphine of 2 : 3. A double-dummy technique was used.

After 3 to 6 days of dosing, the patient visited the Pain Relief Unit before taking his/her morning dose of study medication. The patients took their last dose of CR opioid at approximately 8 p.m. the evening before and they were not allowed to take any escape analgesic doses after midnight. A venous blood sample for the analysis of plasma drug and metabolite concentration was drawn into a 10 ml heparinized tube before dosing (0 h) and at 1 h, 3 h and 5 h after dosing. Prior to each blood sample, the patient also completed a series of pharmacodynamic assessments: pain intensity on a 100 mm visual analogue scale (VASpi) and 4-point verbal rating scale, subjective drug effect questionnaire and Modified Specific Drug Effect Questionnaire (9).

A similar 3 to 6-day period was then completed in a cross-over design using the other opioid, without any washout period.

A debrisoquine test to determine the CYP2D6 phenotype was performed following the method by Wedlund et al. (10).

Table 1

Characteristics of the 27 patients who completed the study

Patient (No.)	Sex	Age (years)	Weight (kg)	Height (cm)	Origin of cancer	Type of pain	Former opioid
1	F	52	74	172	Breast	N	Morphine
2	M	68	80	169	Rectum	B	Morphine
3	F	67	46	153	Oesophagus and maxillary sinus	B	Morphine+ codeine
4	M	69	82	176	Rectum	B	Morphine
5	F	60	65	168	Unknown	V	Morphine
6	F	57	40	161	Lung	B	Morphine
7	M	49	73	176	Pancreas	V	Morphine
8	M	65	82	178	Prostate gland	B	Morphine
9	M	39	76	180	Rectum	V	Morphine
10	M	63	60	176	Kidney	B	Morphine+ d-propoxyphen
11	F	55	64	160	Lung	N	Morphine
12	M	68	64	176	Lung	N	Morphine
13	F	52	75	166	Rectum	N	Morphine
14	F	47	57	166	Ovary	V	Morphine
15	M	59	78	178	Prostate gland	B	–
16	M	76	65	166	Prostate gland	B	d-propoxyphen
17	F	60	50	166	Pancreas	V	Oxycodone
18	M	57	78	171	Prostate gland	B	Morphine
19	M	72	71	183	Prostate gland	B	Morphine
20	M	68	95	182	Prostate gland	B	Methadone
21	M	68	45	176	Lung	B	Oxycodone
22	M	72	80	170	Unknown	B	d-propoxyphen
23	M	69	64	168	Rectum	V	Morphine
24	F	49	51	163	Pancreas	V	Oxycodone
25	M	57	60	176	Pleura	B	Morphine
26	F	52	65	163	Breast	M	Morphine
27	F	50	67	170	Pancreas	V	Oxycodone
Mean (±SEM)		60 (1.8)	66.9 (2.5)	170.7 (1.4)			

Types of pain: N = neuropathic; B = nociceptive (bone metastases); V = nociceptive (visceral); M = mixed.

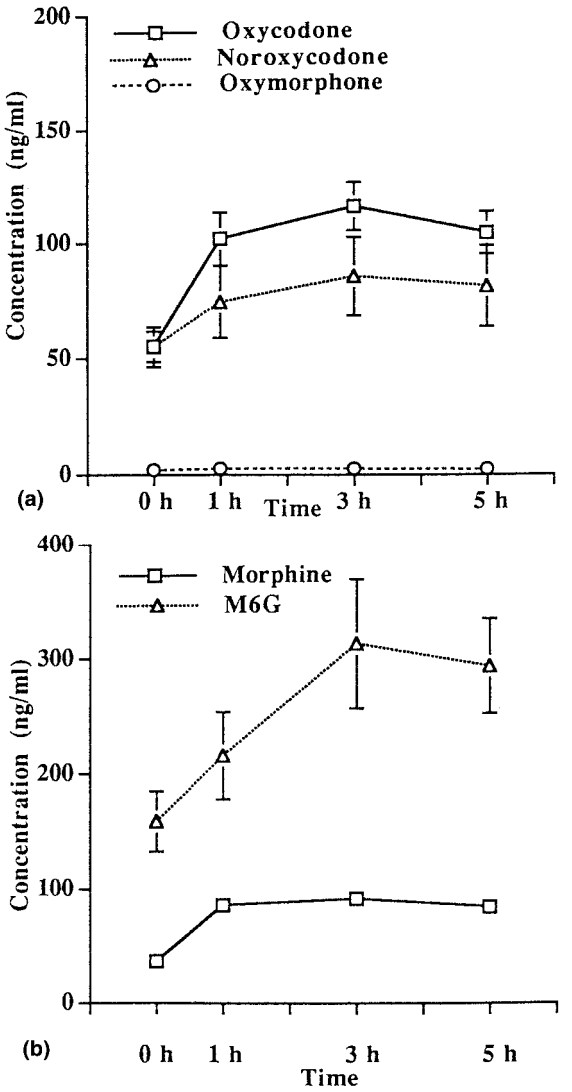

Fig. 1. The mean (±SEM) adjusted concentrations of oxycodone, noroxycodone and oxymorphone a) and morphine and morphine-6-glucuronide (M6G). b) during the PK/PD visit day of. The concentrations are presented as adjusted values: each patient's plasma concentration at each time point was divided by that patient's dose and then multiplied by 120 (morphine) or 80 (oxycodone). Note the different scales on the y-axes: a larger scale for morphine and M6G is necessary because of the high M6G concentrations. The SEM values for morphine are indistinguishable because of the large scale used.

Plasma drug concentration analysis

The blood samples were centrifuged at 3000 rpm and the plasma was stored at −20°C until analysis. The plasma concentrations of oxycodone and noroxycodone were determined in duplicate by gas chromatography (G.C.) as described by Weinstein & Gaylord (11) with the modifications used by Pöyhiä et al. (12).

Oxymorphone was analyzed by G.C. using negative chemical ionization mass spectrometry. Morphine and morphine-6-glucuronide (M6G) concentrations in plasma were determined in accordance with Svensson (13) by high-performance liquid chromatography.

Statistical analysis

Simple regression analysis was used to discern relationships between plasma drug concentrations and VASpi or subjective drug effect ratings. Individual comparisons between the number of escape analgesic doses were performed using the χ^2 test. The plasma drug concentrations at defined time points as well as the VASpi ratings were compared using the paired t-test. Significance was set at $p < 0.05$.

RESULTS

Twenty patients out of 45 were evaluable for analysis (Table 1). The 0 h data of 7 more patients were analyzed, but these patients were excluded from further pharmacokinetic analysis because of use of escape medication after the 0 h sample. A total of 18 patients withdrew or were excluded from the study because of adverse events in the titration phase (7 patients), insufficient pain relief (3), sudden deterioration unrelated to the study (2), incorrect escape analgesic owing to a pharmacy error (1), use of escape medication after midnight on the day of blood sampling (2), non-compliance (2) and suspected incomplete absorption of the drugs (1). Of the 18 patients withdrawn, 11 had been receiving oxycodone and 7 morphine in the titration phase.

The mean total daily dose of oxycodone during the stable phase was 148 ± 18 mg and that of morphine 204 ± 24 mg. The mean plasma concentrations of oxycodone, morphine and their metabolites are indicated in Fig. 1. The oxymorphone concentrations were low, ranging from 0.4 to 10.8 ng/ml, compared with the oxycodone and noroxycodone concentrations, which were in the range of 20 to 290 ng/ml and 10 to 259 ng/ml, respectively. The median ratio of oxycodone to noroxycodone plasma concentrations was 1 : 1.4 at 0 h and 1 : 1.1 at 5 h. The median ratio of oxycodone to oxymorphone concentrations ranged from 33 : 1 at 0 h to 35 : 1 at 5 h.

The median ratios of morphine to M6G concentration were 1 : 6.7 at 0 h and 1 : 5.5 at 5 h. Four patients (mean daily dose of CR morphine 75 mg) had undetectable morphine concentrations at 0 h and their M6G concentrations at the same time were low (median 120 ng/ml vs. 215 ng/ml in all patients). Three of these patients had the lowest unadjusted oxycodone concentrations (< 10 ng/ml) in the study at 0 h as well.

There was no correlation between the visual analogue scale for pain intensity (VASpi) ratings or adverse effects and the plasma opioid concentrations at any time point. The VASpi values during the last day of each stable phase

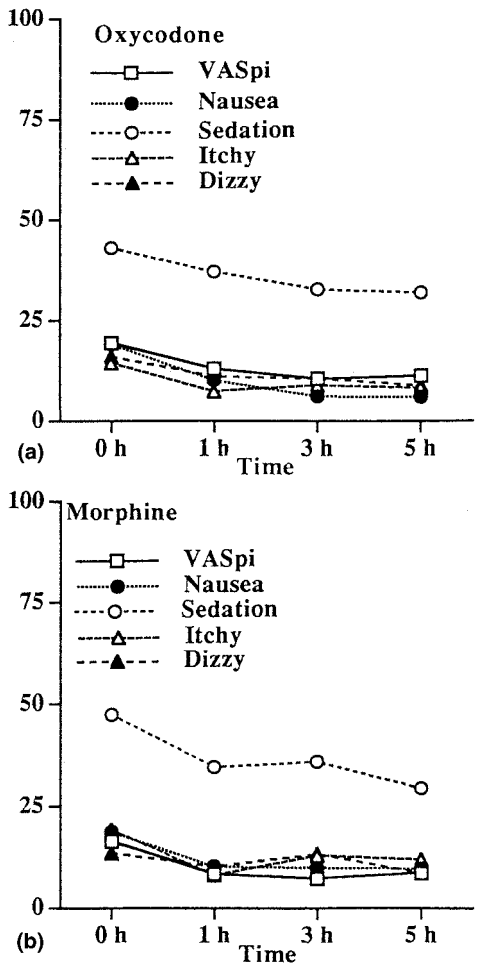

Fig. 2. The mean visual analogue scale ratings for pain intensity (VASpi) and some of the most frequent adverse experiences for oxycodone and morphine. —□— = VASpi; ...●... = nausea; ...○... = sedation; ---△--- = itchy; ---▲--- = dizzy.

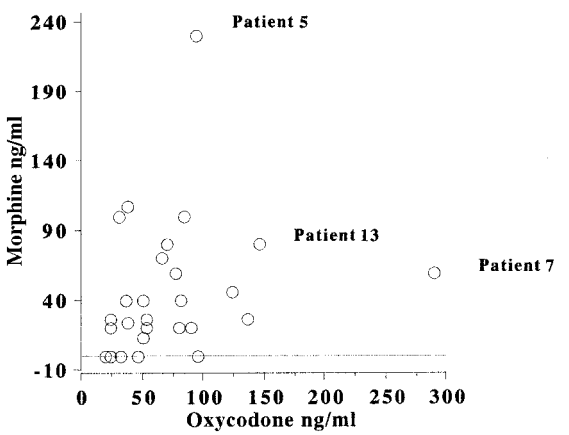

Fig. 3. The individual adjusted plasma concentrations of oxycodone and morphine at 0 h during the PK/PD visit day at the end of each stable phase.

showed no statistically significant differences between the two treatments. An average of only four patients reported a verbal rating score (VRSpi) exceeding 1.0 (slight pain) during the last day of each treatment. The VASpi and some of the most frequent adverse experiences are presented in Fig. 2.

The plasma oxycodone and morphine concentrations did not differ significantly, when the sequence of opioid administration was taken into account. The adjusted plasma morphine concentrations in patients who received morphine in Phase II tended to be lower than those in patients given morphine in Phase I (n.s.).

The individual variations in the adjusted plasma opioid concentrations at 0 h can be seen in the scattergram in Fig. 3. The coefficients of variation for the adjusted plasma morphine concentrations were higher (range 0.52–1.06) than those of oxycodone (range 0.46–0.77).

Two patients with liver dysfunction had plasma opioid concentrations that were markedly different from those of the main study population. Patient 7, a 49-year-old male with pancreatic cancer, had cholestasis which was relieved by a palliative choledochus stent (Table 2). The patient's serum creatinine value was slightly above the normal range. His oxycodone and oxymorphone concentrations were high, whereas the noroxycodone concentration was low (Table 3). He had good pain relief during both oxycodone and morphine medication.

Patient 5, a 60-year-old female, had cancer of unknown origin with liver metastases (Table 2). The patient was on tamoxifen, nifedipine and propranolol as concomitant medications. Her serum creatinine value was within the normal range. Her morphine and M6G concentrations were high, and pain relief during morphine treatment was significantly better than during oxycodone treatment (VASpi 0 mm vs. 70 mm at 0 h). The patient consumed less escape medication during the four days of CR morphine treatment (2 doses) than during CR oxycodone treatment (10 doses).

A debrisoquine test was carried out on 18 patients. Two patients had to be excluded from the debrisoquine test for safety reasons (coronary artery disease), 2 patients were hospitalized for sudden deterioration after the study and 5 patients were not tested for other reasons. One patient, a 52-year-old woman with cancer of the rectum, was a poor metabolizer (PM). Her concomitant medications were metoprolol for hypertension, estradiol + noretisterone acetate for hormone replacement therapy and haloperidol for opioid-induced nausea. The patient's renal function was somewhat decreased because of hydronephrosis of the left kidney with a serum creatinine of 149 ωmol/L (normal range < 115 ωmol/l). Her liver function was normal. The patient had high oxycodone and noroxycodone concentrations and an average oxymorphone concentration. The ratio of oxycodone to noroxycodone plasma concentrations was 1 : 1.6 (median 1 : 1.4 at 0 h) and the ratio of oxycodone to oxymorphone was 77 : 1 (median 33 : 3 at 0

Table 2

Liver and kidney function tests

Test	Normal range	Patient 5	Patient 7	Patient 13 (PM)
ASAT	10–35 U/l (women) 10–50 U/l (men)	245	169	32
ALAT	10–35 U/l (women) 10–50 U/l (men)	118	290	14
AFOS	60–275 U/l	725	1626	113
Creatinine	<115 ωmol/l	111	138	149

Abbreviations: ASAT = aspartate amino transferase; ALAT = alanine amino transferase; AFOS = alkaline fosfatase.

Table 3

Adjusted plasma opioid and metabolite concentrations (ng/ml) and the opioid to metabolite concentration ratios at 0 h

	Median (range)	Patient 5	Patient 7	Patient 13 (PM)
Oxycodone	54 (20–290)	94	290	147
Oxymorphone	2.0 (0.4–10.8)	1.9	10.8	1.9
Oxycodone : oxymorphone	33 : 1	50 : 1	27 : 1	77 : 1
Noroxycodone	73 (10–259)	259	10	243
Morphine	27 (0–230)	230	60	80
M6G	215 (60–700)	430	220	453
Morphine : M6G	1 : 6.7	1 : 1.9	1 : 3.7	1 : 5.6

h). The M6G concentration was high as well. The pain intensity of the patient was higher during oxycodone (VASpi 70 mm) compared with morphine (VASpi 32 mm) treatment at 0 h and she consumed more escape analgesics during oxycodone (4 doses in 4 days) than morphine (no doses) treatment.

DISCUSSION

In the present study, both CR oxycodone and CR morphine provided adequate, stable analgesia, as most of the patients reported their pain as 'slight' or 'none' at the end of the stable phases.

The high number of withdrawals reflects the fact that cancer patients with pain are a challenging group to study. Few randomized, double-blind, cross-over analgesic studies have been published. Hanks et al. (14) reported a high dropout rate (33%), close to that of the present study.

The ratio of morphine to M6G concentrations ranged from 1 : 5.5 to 1 : 6.7, which is in agreement with previous studies (15, 16).The high number of patients with undetectable plasma morphine concentrations prior to the morning drug dosing is probably due to the low daily CR opioid dose in these patients (mean daily morphine dose 75 mg) since three of these patients had very low oxycodone concentrations, too. In previous clinical studies of cancer patients, it has been found that even low daily doses of CR morphine have resulted in measurable plasma morphine concentrations (17, 18) but the assay limit for morphine has been lower (1 ng/ml) (19) than in the present study (5 ng/ml). The low bioavailability (18%) of CR morphine tablets (20) may contribute to the undetectability. In healthy volunteers, a single dose of CR morphine (30 mg) resulted in peak concentrations of 10.7–15.2 ng/ml (21). In cancer patients, however, the steady-state plasma morphine levels may be affected by the disease or other factors (e.g. chronic constipation) that can influence the absorption of CR tablets (15).

Plasma oxycodone concentrations were above the limit of detection (3 ng/ml) even at 0 h and with small daily doses, indicating a slower elimination of oxycodone, consistent with the longer elimination half-life (t 1/2) and better bioavailability of oral oxycodone compared with morphine reported in previous studies (12, 22).

A wide individual variability in the plasma opioid concentrations was evident, as has been reported in previous studies (17, 18, 22). In cancer patients, no simple correlation between opioid and metabolite concentrations and pain relief has been found (19), although Faura et al. (16)

have reported a tendency towards greater stable phase morphine concentrations in cancer patients with optimal pain control.

Morphine and oxycodone are very similar in their pharmacodynamic actions but have different routes of metabolism. Both morphine (morphine-6-glucuronide) (23) and oxycodone (oxymorphone) (24) have metabolites with analgesic efficacy. The role of oxymorphone in the total analgesic effect of oxycodone is, however, not yet clear. Liver dysfunction affects the metabolism of both oxycodone and morphine by increasing the elimination half-life and reducing plasma clearance (25, 26). In kidney failure, oxycodone elimination is prolonged because of increased volume of distribution and reduced clearance (27). Patients with kidney failure have higher morphine concentrations and morphine metabolites tend to accumulate (28). In the present study, the two patients with markedly aberrant plasma opioid concentrations also had liver failure. In patient 7, no clinically significant adverse experiences could be attributed to the high oxycodone and metabolite concentrations, nor were there any differences in pain relief between oxycodone and morphine. The slightly reduced kidney function did not cause morphine or M6G accumulation. Patient 5, however, had excellent pain relief with morphine and high morphine and M6G concentrations, whereas pain relief was poor with oxycodone. The plasma oxycodone, oxymorphone and noroxycodone concentrations of this patient suggest a slow elimination of oxycodone and a diminished metabolism of oxycodone to oxymorphone, evident in the high ratio of oxycodone to oxymorphone (Table 3). This is in agreement with the results of the study by Tallgren et al. (25). These two patients (nos. 7 and 5) were unfortunately not phenotyped for CYP2D6, but the latter patient was taking drugs with a possible inhibitory effect on this enzyme.

The patient with PM phenotype for CYP2D6 had poor pain relief with oxycodone and only an average oxymorphone concentration, whereas her oxycodone and noroxycodone concentrations were high. The ratio of oxycodone to oxymorphone at 0 h was very high (Table 3). The patient's morphine and especially M6G concentrations were high and pain relief was good, possibly owing to the fact that she had minor renal dysfunction.

CONCLUSIONS

Significant variations were found in plasma opioid concentrations in cancer patients with stable opioid medication. The variation in plasma opioid concentrations was greater with morphine, consistent with the lower bioavailability of morphine compared with oxycodone. Liver dysfunction, renal insufficiency or poor metabolizer phenotype for CYP2D6 affecting the production and elimination of active metabolites should be taken into account when choosing opioid treatment in cancer-related pain. The role of oxymorphone in oxycodone analgesia needs to be clarified. It is important to monitor the dosing of oral opioids closely even after the initial titration phase, and also when switching from one opioid to another.

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