A randomised, double-blind, parallel group, multicentre study to compare the tolerability, safety, and efficacy of oxycodone with morphine in patients using i.v. patient-controlled analgesia (PCA) for acute postoperative pain

[OXI3201]

Objectives

The aim of the study was to compare the efficacy, tolerability, and safety of i.v. PCA oxycodone with i.v. PCA morphine in patients with acute postoperative pain.

Patients and methods

This was a randomised, double-blind study. Patients who were due to have surgery and were expected to have acute postoperative pain needing between one and three days' treatment with i.v. PCA were enrolled. Patients were allocated to treatment just before their surgery started. Treatments used for i.v. PCA were oxycodone hydrochloride solution 10 mg/ml and morphine sulphate solution 10 mg/ml, both of which were diluted to a concentration of 1 mg/ml in 0.9% saline before use.

Immediately after surgery, patients were stabilised with 2 mg i.v. bolus doses of their allocated study medication and were then transferred to PCA for 24 to 72 hours. The PCA machine was set up to deliver bolus doses of 1 mg on demand with a lockout period of 5 minutes. In addition to their study medication, patients also received diclofenac 50 mg three times daily (suppositories or tablets, as appropriate).

Patients recorded their pain intensity at rest and on movement or deep breathing using the box scale-11 (BS-11) scale. They recorded scores before stabilisation, before starting i.v. PCA, at 2, 4, 8, 24, 36, 48, 60, and 72 hours after surgery, and when they completed or discontinued from the study.

In addition, the investigator recorded the patient's use of study medication throughout the study, and patients recorded sleep disturbance and quality of sleep on a daily basis, and rated their satisfaction with their postoperative pain relief at completion or discontinuation.

The investigator recorded any adverse events and reactions at the infusion sites, and measured the patient's vital signs.

This was an equivalence study, so the per-protocol (PP) population was considered to be the most important. Demographic and tolerability data are presented for the intent-to-treat (ITT) population.

Results

One hundred and forty-eight patients were enrolled and 133 were treated with oxycodone (n = 64) or morphine (n = 69). Over 85% of patients in each treatment group were female. The mean (standard deviation) age of patients was 47.5 (13.16) years in the oxycodone group and 48.7 (11.96) years in the morphine group. All patients had undergone general surgery, mainly hysterectomy, breast surgery, or laparoscopy and/or laparotomy.

Efficacy

Patients' pain scores on movement or deep breathing and at rest showed a general decreasing trend over time. There were some increases in the pain scores on movement or deep breathing in the morphine group beyond 36 hours after surgery, but this could be because of the low numbers of patients remaining in the study. The table below shows the BS-11 pain scores, treatment differences, and 95% confidence intervals (CIs) at 4 and 24 hours after surgery, and at completion and discontinuation for the PP population. The 95% CIs for the treatment differences were within the limits accepted for equivalence, including those for the primary efficacy endpoint (pain on movement or deep breathing at 24 hours after surgery).

	Mean (SD) score				Treatment difference	
	Oxycodone (n = 46)*		Morphine (n = 54)*		(95% CI)	
Movement or deep breathing:						
4 hours	5.1	(2.29)	5.0	(2.09)	0.05	(-0.82, 0.92)
24 hours	4.6	(2.64)	4.1	(2.02)	0.55	(-0.37, 1.48)
Completion or discontinuation	3.2	(2.17)	3.5	(2.24)	-0.31	(-1.27, 0.64)
Rest:						
4 hours	3.2	(1.99)	3.4	(1.78)	-0.23	(-0.98, 0.51)
24 hours	2.1	(1.82)	1.5	(1.31)	0.65	(0.02, 1.27)
Completion or discontinuation	1.5	(1.74)	1.3	(1.40)	0.26	(-0.42, 0.94)

*For pain at 4 hours and at completion or discontinuation, numbers of patients with data available were 40 in the oxycodone group and 45 in the morphine group.

The median (range) total use of study medication was 69.0 (12 – 336) mg in the oxycodone group and 54.0 (7 – 212) mg in the morphine group. This treatment difference was not statistically significant. The dose ratio for oxycodone:morphine was 1.3:1. The mean (SD) total number of demands from the PCA machine was 138.8 (161.7) in the oxycodone group and 84.4 (81.02) in the morphine group. The

mean (SD) number of successful demands was 70.9 (46.6) in the oxycodone group and 53.2 (36.9) in the morphine group.

During the first night after surgery, 25 patients (54%) in the oxycodone group and 28 (53%) in the morphine group were not woken because of pain. Quality of sleep was also similar in the two groups, with approximately half the patients in each group reporting that their quality was at least fair.

Forty patients (87%) in the oxycodone group and 54 patients (100%) in the morphine group were satisfied or very satisfied with their postoperative pain relief.

Tolerability

Fifty patients (78%) receiving oxycodone and 57 (83%) receiving morphine had at least one adverse drug reaction [(ADR), i.e. an AE that the investigator considered to be related to treatment or in which he/she recorded the relationship as not determined or not assessable]. The most common ADRs (i.e. those reported by at least 10% of patients in either treatment group) are shown in the table below.

	Number (%) of patients				*P* value for treatment difference
	Oxycodone (n = 64)		Morphine (n = 69)		
Nausea	32	(50)	45	(65)	0.076
Vomiting	11	(17)	6	(9)	0.143
Constipation	3	(5)	10	(14)	0.057
Pruritus	9	(14)	5	(7)	0.201

Pain, swelling, erythema, and leakage at the infusion site were not common in either treatment group. At 24 hours after surgery and at completion or discontinuation, less than 5% of patients in both groups had swelling, erythema, or leakage at the infusion site. At 24 hours after surgery, four patients (7%) in the oxycodone group had pain at the infusion site, but this decreased to two patients (3%) at completion or discontinuation; the percentage of patients in the morphine group with pain at the infusion site was 1% at both times.

Some patients had changes in their vital signs that resulted in values after surgery that were outside of the normal ranges. However, none of these were unexpected in patients who had undergone surgery.

Discontinuations

Eight patients (13%) in the oxycodone group discontinued because of adverse events (n = 4), protocol violation (n = 1), or ‘other’ (n = 3). Eight patients (12%) in the morphine group discontinued because of adverse events (n = 5) or ‘other’ (n = 3).

Conclusions

Oxycodone was as effective as morphine in controlling patients’ postoperative pain when administered by i.v. PCA, and the tolerability of the two treatments was similar. Intravenous PCA oxycodone is an effective alternative to i.v. PCA morphine for treating pain in the immediate postoperative period.