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The pharmacokinetics of oxycodone after intravenous injection in adults

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Oxycodone chloride (0.07 mg kg^{-1}) was given by intravenous bolus to nine young adult surgical patients on the first postoperative day. Plasma was sampled for up to 12 h. Mean values of $t_{½z}$, CL and V_{ss} were 222 min, 0.78 l min^{-1} and 2.60 l kg^{-1}, respectively. The concentrations of the metabolite noroxycodone was also measured. The mean AUC(0,12) ratio of noroxycodone to oxycodone was 0.33. Oxymorphone was not detected.

Keywords oxycodone oxymorphone noroxycodone pharmacokinetics

Introduction

Oxycodone (14-hydroxy-7,8-dihydrocodeinone) is a semi-synthetic opioid, with effects similar to those of morphine (Kalso *et al.*, 1990, 1991; Saarialho-Kere *et al.*, 1989). Noroxycodone (Weinstein & Gaylord, 1979) and oxymorphone (Baselt & Stewart, 1978) are thought to be the main metabolites of oxycodone in man. Although oxycodone has been in clinical use since the 1920s, its pharmacokinetics have not been investigated in detail. We have studied the kinetics of oxycodone after i.v. injection in young adults after minor abdominal surgery.

Methods

After approval by the Institutional Ethics Committee informed consent was obtained preoperatively from nine patients scheduled for appendicectomy. The patients were otherwise healthy and did not receive any medication except for pre-, peri- and postoperative anaesthetic/analgesic drugs. This open single dose study of oxycodone was performed on the first postoperative day. The demographic data of the patients are shown in Table 1. Patients with known or suspected intolerance or allergy to analgesics and with diagnoses other than acute appedicitis were excluded.

Anaesthetic procedure and administration of oxycodone

The patients were premedicated with pethidine (1 mg kg^{-1} i.m.). Balanced anaesthesia consisted of thiopentone (3–5 mg kg^{-1}) or propofol (1 mg kg^{-1}), glycopyrrolate, suxamethonium and vecuronium, enflurane and nitrous oxide/oxygen (2:1), and alfentanil or fentanyl. After completion of surgery neuromuscular blockade was reversed with neostigmine and glycopyrrolate. Pethidine and diclofenac were given when requested for postoperative pain.

On the first postoperative morning an intravenous cannula (Venflon, Viggo®, Sweden) was inserted into an antecubital vein of the right arm for blood sampling. Oxycodone chloride (Oxanest®, 10 mg ml^{-1}, Leiras, Finland) was given in a dose of 0.07 mg^{-1} kg^{-1} (= 0.05 mg^{-1} kg^{-1} free base) via an intravenous cannula in the left arm. After the injection the cannula was flushed with 20 ml of 0.9 % saline. Venous blood samples (5 ml) were collected into chilled heparinized plastic tubes before the oxycodone was given and at 5, 10, 15, 20, 25, 30, 45, 60 and 90 min and 2, 3, 4, 5, 6 and 12 h after injection. The plasma was separated immediately and stored at −20° C until analysis. The patients stayed in the supine position for 3–4 h, after which a light meal was served.

Assays and pharmacokinetic analysis

Plasma oxycodone concentrations were measured by gas chromatography as described by Kalso *et al.* (1990). The lower limit of the oxycodone assay was 3 ng ml^{-1}. Plasma noroxycodone was measured as a heptafluorobutyric acid anhydride derivative by gas chromatography using a method modified from Weinstein & Gaylord (1979). Toluene was used for extraction and flurazepam served as internal standard. The assay limit was 1 ng ml^{-1} and the intraday variation, expressed as C.V.%, for successive analyses of pooled plasma was 8% (30 ng ml^{-1}, $n = 7$).

Plasma oxymorphone was assayed by an h.p.l.c. method (Pöyhiä *et al.*, in preparation). In brief, oxymorphone was extracted with washed butylacetic acid and 0.1 M perchloric acid using naltrexone as internal standard. Separation was achieved isocratically at room temperature using a 100 × 3.2 mm Velosep RP-18

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Table 1 Characteristics of the patients, durations of anaesthesia, time from the end of the anaesthesia to the administration of oxycodone (time to study), pharmacokinetic parameters of oxycodone and the ratio of AUC(0,12) of noroxycodone to that of oxycodone (AUC ratio). Mean values, s.d. and 95% confidence intervals (95% C.I.) are shown

Patient and sex	*Age (years)*	*Weight (kg)*	*Height (cm)*	*Duration of anaesthesia (min)*	*Time to study (h)*	*Dose (mg)*	$t_{½,z}$ *(min)*	V_{ss} *(l kg^{-1})*	*CL (l min^{-1})*	*AUC ratio (nor/ox)*
1 M	29	75	176	70	12.8	4.1	227	2.12	0.59	0.14
2 F	37	78	176	80	7	4.3	110	2.44	1.33	0.83
3 M	30	90	178	60	15.6	4.7	159	2.83	1.22	0.43
4 F	31	80	176	60	11	4.3	219	2.40	0.66	0.30
5 M	24	76	180	60	8	4.1	580	3.65	0.38	0.06
6 M	27	61	180	50	13.3	3.1	154	2.74	0.82	0.46
7 F	19	62	179	50	15.4	3.1	194	2.84	0.92	0.42
8 F	28	61	175	50	19	3.1	175	2.56	0.64	0.19
9 F	22	57	166	35	15.8	3.1	177	1.83	0.45	0.17
Mean	27	71	175	57	13.1	3.8	222	2.60	0.78	0.33
s.d.	5.3	11	5.2	13	3.9	0.6	139	0.52	0.33	0.23
95% C.I.	23–32	63–80	173–179	47–67	10.1–16.1	3.3–4.3	115–329	2.21–3.00	0.53–1.03	0.15–0.51

(Brownlee Labs, USA; 3 μm) column and a mobile phase consisting of 15% (v/v) acetonitrile and 4.5, 1.0 and 1.0 g l^{-1} of monochloracetic acid, heptanesulphonic acid and tetraethylamine, respectively. A coulometric detector with a dual electrode (Esa Coulochem Model 5100 A) was used with upstream oxidation at 0.2 V and downstream oxidation of eluate at 0.5 V. The assay limit was 0.5 ng ml^{-1} and the C.V. % was less than 5% for 8 successive analyses at a concentration of 2.2 ng ml^{-1} (intraday variation).

Drugs administered before or during anaesthesia or in the postoperative phase (see Methods) did not interfere with the analyses. Several benzodiazepines and phenothiazines were also tested and found not to interfere with the assay.

Individual plasma drug concentration-time profiles were fitted by bi- and triexponential functions using nonlinear least-squares regression (Wilkinson, 1988). The measured concentration values were weighted equally. The goodness of fit was determined by Akaike's information criterion (Akaike, 1976) and by assessment of randomness of 'scatter' of actual data points about the fitted function. Values of elimination half-life ($t_{½,z}$), steady-state volume of distribution (V_{ss}) and clearance (CL) were calculated by standard methods (Wagner, 1976). The ratio of the area under the plasma noroxycodone concentration-time curve from 0 to 12 h (AUC(0,12)) to the corresponding area under the plasma oxycodone concentration-time curve was calculated. AUC was estimated using the linear trapezoidal rule. Data are presented as mean values with standard deviations and 95% confidence intervals.

Results

The plasma concentrations of oxycodone were described best by a biexponential function in six patients and by a triexponential function in three patients (1, 5 and 7). The calculated pharmacokinetic parameters are shown in Table 1. None of the kinetic parameters correlated with age, body weight or the duration of anaesthesia.

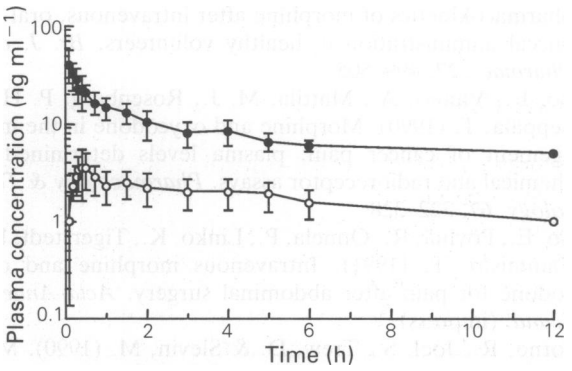

Figure 1 Semilogarithmic plot of mean (± s.d.) plasma oxycodone (•) and noroxycodone (○) concentrations after intravenous administration of oxycodone to nine adults.

The peak concentration of noroxycodone (mean and range: 4.1; 3–8 ng ml^{-1}) was reached in 22 (range: 10–30) min. The time courses of plasma oxycodone and noroxycodone concentrations are shown in Figure 1. Oxymorphone was not detected in the plasma.

Discussion

Oxycodone and morphine are the most commonly used opioids in Finland. Although oxycodone has been regarded as an alternative to morphine with similar potency and duration of action there are few studies of its pharmacology in man (Kalso *et al.*, 1990, 1991; Saarialho-Kere *et al.*, 1989). In the present study the mean elimination half-life of oxycodone was found to be 3.7 h. This is longer than that reported for morphine (1.7–1.9 h) in healthy volunteers (Hoskin *et al.*, 1989; Osborne *et al.*, 1990). This difference reflects a lower clearance of oxycodone since the volumes of distribution of the drugs are similar. The study was carried out at about 13 h after surgery, as general anaesthesia may interfere with the pharmacokinetics of many drugs. The present results are in agreement with our previous findings demonstrating that the duration of the analgesic effect of intravenous

oxycodone after abdominal surgery is longer than that of intravenous morphine (Kalso *et al.*, 1991).

It has been suggested that some of the analgesic effect of oxycodone might be due to its active metabolites (Kalso *et al.*, 1990). Conjugated oxymorphone and oxycodone, free oxycodone and noroxycodone have been measured in human urine after oral oxycodone (Baselt & Stewart, 1978; Weinstein & Gaylord, 1979). In the present study noroxycodone concentrations were very low. According to Weinstein & Gaylord (1979), noroxycodone is a considerably weaker analgesic than oxycodone in the dog. Oxymorphone, which is another metabolite of oxycodone (Baselt & Stewart, 1978), is known to be a potent analgesic. However, plasma concentrations of this metabolite were always below the assay limit (0.5 ng ml^{-1}).

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