Pharmacological Reports 66 (2014) 153–158

Contents lists available at ScienceDirect

Pharmacological Reports

journal homepage: www.elsevier.com/locate/pharep

Original research article

Pharmacokinetics of oxycodone hydrochloride and three of its metabolites after intravenous administration in Chinese patients with pain

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ARTICLE INFO

Article history:
Received 23 October 2012
Received in revised form 29 July 2013
Accepted 13 August 2013
Available online 1 February 2014

Keywords:
Oxycodone
Metabolites
Pharmacokinetics
Chinese patients with pain

ABSTRACT

Objectives: The aim of this study is to evaluate the pharmacokinetic profile of oxycodone and three of its metabolites, noroxycodone, oxymorphone and noroxymorphone after intravenous administration in Chinese patients with pain.
Methods: Forty-two subjects were assigned to receive intravenous administration of oxycodone hydrochloride of 2.5, 5 or 10 mg. Plasma and urine samples were collected for up to 24 h after intravenous administration of oxycodone hydrochloride.
Results: Pharmacokinetic parameters showed that mean values of C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ of oxycodone were dose dependent, whereas T_{max} and $t_{1/2}$ were not. The mean AUC_{0-t} ratio of noroxycodone to oxycodone ranged from 0.35 to 0.42 over three doses, and those of noroxymorphone, or oxymorphone, to oxycodone were ranging of 0.06–0.08 and 0.007–0.008, respectively. Oxycodone and its three metabolites were excreted from urine. Approximately 10% of unchanged oxycodone was recovered in 24 h. Most adverse events (AEs) reported were mild to moderate. The frequently occurred AEs were dizziness, nausea, vomiting, drowsiness and fatigue. No dose-related AEs were found.
Conclusion: Our pharmacokinetics of oxycodone injection in Chinese patients with pain strongly support continued development of oxycodone as an effective analgesic drug in China.

Introduction

Oxycodone, a semi-synthetic opioid analog, is widely used to treat the moderate or severe degrees of cancer pain [11], postoperative pain [18] and neuropathic pain [20]. Oxycodone is a μ- and κ-opioid receptor agonist and has similar pharmacologic effects with morphine [6,10]. In oral administration, oxycodone has shown a bioactivity 1.5- to 2-folds higher than that of morphine [2], but the side effects such as nausea and hallucinations less than those of morphine [7].

Pharmacokinetic studies indicated that after intravenous administration, oxycodone shows a mean terminal half-life ($t_{1/2}$) of 3.7–5.5 h [12,18], which is comparable with that of oral administration (3.5–5.1 h) [13,19]. The mean dose-normalized area under the concentration–time curve AUC is also similar to that after receiving oral oxycodone tablets, whereas the latter can be affected by food and general anesthesia [6]. Oxycodone is extensively metabolized in liver. The major fraction of oxycodone is N-demethylated by CYP3A4 to noroxycodone. A smaller fraction of oxycodone is O-demethylated to oxymorphone by CYP2D6. Further oxidation of these metabolites yields noroxymorphone. Some other reductive and conjugated glucuronides are also discovered [15]. Among these metabolites, noroxycodone has weak affinity to μ-opioid receptor [3], whereas oxymorphone has analgesic potency approximately 10-folds more than that of morphine [1]. These metabolites are excreted from urine. Most of oxycodone and noroxycodone are excreted as their free forms, whereas oxymorphone is mainly excreted in a conjugated form [19].

Oxycodone entered into clinical practice since 1917, and to date, various formulations had been developed, including oral immediate- and controlled-release formulations, intravenous ampouls as well as combination formulations, for example, together with paracetamol [14]. In China, oxycodone is only available in the form of oral controlled-release tablets. Although oral administration is the most preferred route by patients, alternative route is considerable when patients have gastrointestinal disease or difficulty in swallowing, or when patients have great and acute pain or poor pain control. The intravenous administration is a commonly used as an alternative for these

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http://dx.doi.org/10.1016/j.pharep.2013.08.012

individuals. However, there are no pharmacokinetic data of intravenous administration of oxycodone reported in Chinese people. The aim of this study is to determine the pharmacokinetics of oxycodone and three of its metabolites after intravenous administration to Chinese patients with pain.

Materials and methods

Ethics

This study was conducted in accordance with the Declaration of Helsinki [21] and the requirements described in Chinese Good Clinical Practice. The protocol was approved by the Ethic Committee of affiliated Hospital of the Academy of Military Medical Sciences. All the participants provided written informed consent and agreed to the study protocol.

Study participants

The subjects were aged 30–60 years old with a body mass index (BMI) of 19–24 kg/m^2 and a minimum weight of 45 kg. They were breast or colorectal cancer patients with pain and rheumatic patients with chronic musculoskeletal pain. All subjects had the Karnofsky Performance scale score greater than 70 and their survival periods were expected longer than three months. Participants were inclusive if they had not taken opioid medicines within the three months prior to study. In addition, all the participants were required to have hepatic function with ALT or AST level less than 2-folds of normal values and were required to have renal function with the value of total bilirubin, blood urea nitrogen and creatinine level less than 1.25-folds of upper limit of normal value. They were also required to have normal electrocardiogram without clinically significant abnormalities. The patients were excluded if they had hypersensitivity to opioid analgesic agents, had a history of drug or alcohol abuse, had treatment with daily prescribed medications on opioids, or had treatment with monoamine oxidase inhibitors for two weeks before the study initiation day. The subjects were excluded if they had participated in other drug trials within previous two months, had given blood donations of 400 mL or more within three months or 200 mL or more within one month previously. Female subjects were excluded if they were pregnant. In addition, subjects were required to have a negative urine test for drugs such as opiates, barbiturates, amphetamine, cocaine, methadone, benzodiazepines and cannabinoids. Eligible patients signed an informed consent and were given detailed instruction of the study.

Study design and treatments

This was a single dose and parallel-group trial in Chinese patients with pain. The subjects were divided into three groups, respectively named as A, B, C. The doses of administration of oxycodone in the three groups were 2.5 mg, 5 mg and 10 mg, respectively. The oxycodone hydrochloride injection was diluted in 0.9% sodium chloride to 10 mL. Then the solution was infused over two minutes into the forearm of the patient. For safety, the dose of 2.5 mg oxycodone was administrated firstly. After the study of 2.5 mg dose group completed, the dose of 5 mg oxycodone was then given. The dose of 10 mg oxycodone was administrated after the end of the study of 5 mg dose group. About 4 h after drug administration, standard meals were offered and until 24 h after administration, alcohol and coffee were prohibited.

Pharmacokinetic sampling

About 4 mL of blood samples were collected from an indwelling venous catheter into heparinized vacutainers prior to dosing and 0 min, 2 min, 5 min, 10 min, 15 min, 30 min, 45 min, 1 h, 1.5 h, 2 h, 3 h, 4 h, 6 h, 8 h, 12 h, 24 h after drug administration. Samples were inverted slightly and then centrifuged at 1500 × *g* for 10 min at 4 °C. The resulting plasma was transferred to screw-caped tubes. Within 60 min of collection, plasma samples were frozen at −20 °C and kept for analysis.

Urine samples were obtained before dosing and at pooled intervals of 0–2, 2–4, 4–8, 8–12, 12–24 h after drug administration. Urine sample in each interval was mixed, and the total volume was recorded. Aliquots of 5 mL was collected into containers and stored at −20 °C.

Bioanalytical methods

Plasma concentrations of oxycodone, noroxycodone, oxymorphone and noroxymorphone were determined with liquid chromatography with tandem mass spectrometric (LC–MS/MS) method. The plasma samples were prepared by the reported method in our previous research with minor modification [5]. The samples were extracted with Empore MPC-SD, high performance extraction disk plate (3M Company, USA). After been activated, the extraction disk plate was loaded with 2 × 300 μL of plasma spiked with IS and 0.1% trifluoroacetic acid, followed by a serial of elution and extraction. The final elution was evaporated to dryness and then reconstituted with 200 μL of acetonitrile with 0.1% formic acid (0.2% formic acid solution and 20 mM ammonium formate, 9:1, v:v). An aliquot of 50 μL of dissolved residue was applied to LC–MS/MS for analysis. HPLC separation was achieved with an Agilent 1200 LC system. Chromatography was performed on Kromasil 100-5SIL-Dimensions C_{18} column (2.1 mm × 100 mm, 5.0 μm, Thermo Hypersil-Keystone, USA) with 0.75 mL min^{-1} flow rate. The mobile phase consisted of (A) 0.2% formic acid solution containing 20 mM ammonium formate, (B) acetonitrile solution containing 0.1% formic acid. The elution procedure was as follows: 0–0.3 min 95% (B); 0.3–1.0 min, 95–88% (B); 1.0–3.6 min 88% (B); 3.6–3.7 min, 88–95% (B); 3.7–6.5 min, 95% (B). Mass spectrometry analysis was operated with an API 3000 MS/MS system (Applied Biosystems, USA) equipped with electrospray ionization source (ESI). The scan was operated in positive and multiple reaction monitoring (MRM) mode. The parameters of scan were as follows: 2000 V of spray voltage; 540 °C of ion source temperature; 7 psi of GS1 pressure and 12 psi of GS2 pressure; 38 V of collision energy for oxycodone, 40 V for noroxycodone, 39 V for oxymorphone and 40 V for noroxymorphone. Quantification was performed based on the transitions of *m/z* 316.2 → 241.1, 302.2 → 227.1, 302.2 → 227.1, 288.1 → 213.0, 319.2 → 244.0, 305.2 → 230.2, 305.2 → 230.2 and 293.1 → 216.0 for oxycodone, noroxycodone, oxymorphone, noroxymorphone, oxycodone-D3, noroxycodone-D3, oxymorphone-D3, and noroxymorphone-D9, respectively. The analytical range of the assay for oxycodone, noroxycodone, oxymorphone and noroxymorphone were all 0.1–50.0 ng/mL. The lower limit of quantitation (LLOQ) of all of the four compounds was 0.1 ng/mL.

Urine analysis was similar with plasma. Aliquots of 250 μL of mixture containing 50 μL of urine sample, 100 μL of IS solution and 100 μL of 0.1% trifluoroacetic acid was applied to extraction disk plate, which had been conditioned in advance. The following process was the same as that of plasma. The calibration curve of urine samples was ranged from 5.0 to 500.0 ng/mL for oxycodone and noroxycodone, 1.0 to 100.0 ng/mL for oxymorphone, and 2.5 to 250.0 ng/mL for noroxymorphone, respectively. The LLOQ of oxycodone, noroxycodone, oxymorphone and noroxymorphone were 5.0 ng/mL, 5.0 ng/mL, 1.0 ng/mL and 2.5 ng/mL, respectively.

Safety assessment

Vital signs including blood pressure, pulse rate, respiratory rate and temperature were monitored before the drug administration, during the trials at 2, 4, 6 and 24 h after drug administration and at the end of study. Physical examination and ECG were also performed before the drug administration and at 24 h after drug administration. Hematology, serum chemistry and urinalysis test were performed before the drug administration and at the end of study. Adverse events (AEs) were recorded throughout the trial. The principle investigators assessed the severity of AEs and the correlations with the various kinds of treatments.

Statistics

The maximum plasma drug concentration (C_{max}) and the time needed to reach the maximum concentration (T_{max}) were obtained from direct observation of the data. The area under the concentration–time curve (AUC) was calculated both from time zero to infinity ($AUC_{0-\infty}$) and from time zero to the last measurable concentration (AUC_{0-t}). The concentration–time data were analyzed by non-compartmental method in WinNonlin professional Version 6.1 (Pharsight Corporation). The clearance of metabolite (CL_m) was calculated from $CL_m = CL \times \%\ dose \times 10^{-2}$, where CL is the oxycodone clearance and % dose is the percentage of the dose of individual metabolites excreted in urine over 0–24 h. The AUC_{0-t} ratio of metabolite to parent drug was calculated to assess the relative amount of each metabolite in circulation. The pharmacokinetic parameters were analyzed for differences between treatments using an analysis of variance (ANOVA) model with single factor. Statistical significance was set at $p < 0.05$.

Results

Experimental design

Forty-four subjects were enrolled in the study. Two subjects were excluded because of unqualified physical examination before drug dose. The rest of forty-two subjects all completed the study and were included in the safety assessment. Among the forty-two subjects, ten subjects were excluded from pharmacokinetic analysis because of blood sampling in the forearm of receiving drug infusion. The demographics and characteristics of subjects included in the safety assessment and included in pharmacokinetic analysis were separately shown in Tables 1 and 2.

Table 1
Demographics and characteristics of subjects included into the safety assessment.

Characteristics	Subjects in this study ($n = 42$)
Gender, *n* (%)	
Male	20 (48)
Female	22 (52)
Age, yrs	
Mean (SD)	41.80 (10.21)
Range	23–60
Race, *n*%	Han (100)
Height, m	
Mean (SD)	1.63 (0.08)
Range	1.46–1.81
Weight, kg	
Mean (SD)	61.23 (6.75)
Range	49.5–81
BMI, kg m^{-2}	
Mean (SD)	23.11 (2.32)
Range	19.10–28.55
Type of pain, *n* (%)	
Cancer pain	27 (64)
Musculoskeletal pain	15 (36)

Table 2
Demographics and characteristics of subjects included into pharmacokinetic analyses.

Characteristics	Study groups included into pharmacokinetic analysis		
	2.5 mg dose group ($n = 9$)	5 mg dose group ($n = 11$)	10 mg dose group ($n = 12$)
Gender, *n* (%)			
Male	5 (56)	6 (55)	9 (75)
Female	4(44)	5 (45)	3 (25)
Age, yrs			
Mean (SD)	45.2 (9.7)	41.0 (9.8)	38.80 (6.3)
Range	31–60	30–59	30–51
Race, n%	Han (100)	Han (100)	Han (100)
Height, m			
Mean (SD)	1.65 (0.08)	1.63 (0.09)	1.64 (0.06)
Range	1.56–1.81	1.46–1.79	1.54–1.74
Weight, kg			
Mean (SD)	61.3 (8.3)	59.7 (4.9)	62.2 (4.7)
Range	49.5–72.0	50–69	55–70
BMI, kg m^{-2}			
Mean (SD)	20.5 (1.6)	21.7 (1. 8)	22.5 (0.9)
Range	19.1–25.9	19.3–26.1	20.8–24.6
Type of pain, *n* (%)			
Cancer pain	9 (100)	5 (45)	3 (25)
Musculoskeletal pain	0	6 (55)	9 (75)

Pharmacokinetics

The mean plasma concentration of oxycodone and three of its metabolites after intravenous administration of 2.5, 5 or 10 mg of oxycodone hydrochloride to patients with pain were shown in Fig. 1. Table 3 presents a summary of pharmacokinetic parameters. The pharmacokinetics was found to be linear over three doses. Mean values for C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ of oxycodone, noroxycodone, oxymorphone and noroxymorphone increased in a dose-proportional manner. T_{max} values of oxycodone and its three metabolites were independent of doses. Although the T_{max} values of the four compounds in 2.5 mg of dose group were shown higher than those of other two groups, no statistical difference was observed.

The mean $t_{1/2}$ of oxycodone, noroxycodone, oxymorphone and noroxymorphone was also independent of doses. The $t_{1/2}$ values of oxycodone and noroxycodone in 2.5 mg of dose group were higher than those of other two groups. However, no significant difference was observed. Oxymorphone $t_{1/2}$ in the 2.5 mg dose group was not calculated because of frequent concentrations below the limit of the assay. In addition, the values of $t_{1/2}$ of three metabolites were all longer than that of oxycodone. Noroxymorphone had the longest $t_{1/2}$ which was ranging from 11.98 to 13.88 h over the three doses.

The plasma concentrations of the three metabolites were all lower than those of parent drug. Noroxycodone was the most abundant metabolite, which had a mean AUC ratio of ranging from 0.34 to 0.42 over the three doses. Noroxymorphone and oxymorphone had lower concentrations with a mean AUC ratio ranged from 0.06 to 0.08 and 0.007 to 0.008, respectively, among the three dose groups.

The CL of oxycodone among the three dose groups was 37.57 ± 15.85, 42.42 ± 10.44, 44.92 ± 9.4 L/h, respectively, which was not significantly different. The CL_m value was also comparable over the three doses. Cumulative urinary excretion was measured over a 24-h period. Approximately 10% of unchanged oxycodone was recovered.

Safety results

A total of 58 AEs were reported by 24 (57%) of the 42 subjects in this study. The five most common AEs were dizziness (18 subjects,

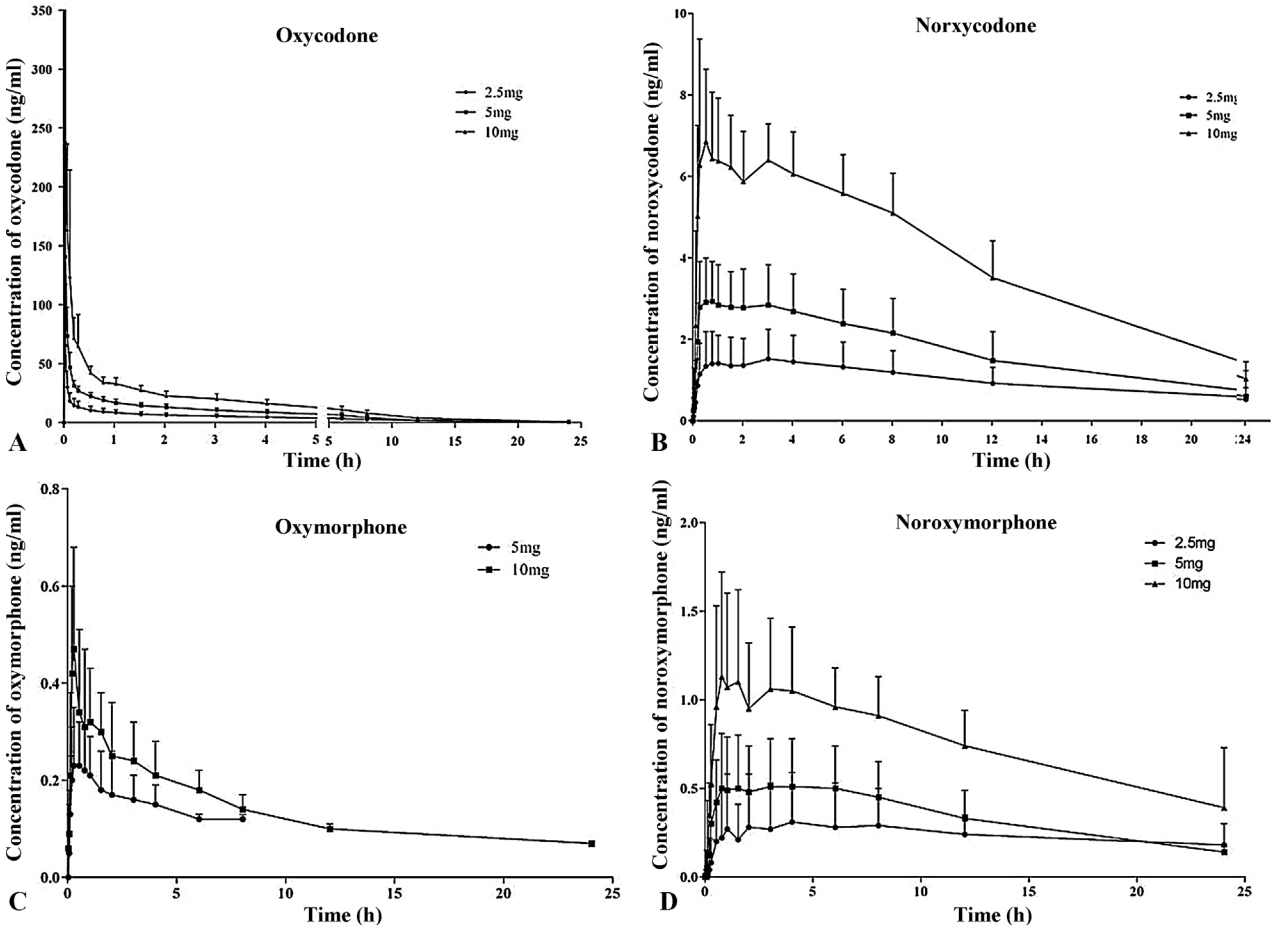

Fig. 1. Mean plasma concentration–time profile of oxycodone (A), noroxycodone (B), oxymorphone (C) and noroxymorphone (D) after intravenous administration of 2.5, 5 or 10 mg of oxycodone to Chinese patient with pain.

75%), nausea (10 subjects, 41. 7%), vomiting (9 subjects, 37.5%), drowsiness (5 subjects, 20.8%), and fatigue (5 subjects, 20.8%). One subject had severe dry mouth and was not given treatment. Two subjects had moderate nauseas and vomiting, with the treatment of intramuscular administration of metoclopramide and diphenhydramine. No other medications were administrated during the study. The majority of AEs was mild and none of these events was dose related. These events were consistent with those expected from the administration of opioid analgesics. No death and no serious events were reported. No clinically significant changes of vital sign and laboratory examination were observed during this study.

Discussion

Since it was introduced to clinical practice in the early 20th of century, oxycodone has been widely used in many countries. Many studies were carried out to investigate the pharmacological characteristics of oxycodone. However, there are no reported studies about pharmacokinetic profile of oxycodone in Chinese people. The purpose of this study was to evaluate the pharmacokinetic profile of oxycodone after the administration of oxycodone hydrochloride injection in Chinese patients with pain. It was the first description of pharmacokinetic characteristics of oxycodone in Chinese patients.

In this study, oxycodone exhibited linear dynamic characteristics. Increasing doses of oxycodone resulted in proportional increases of C_{max} and AUC, while T_{max} and $t_{1/2}$ was unchanged. These pharmacokinetic parameters of oxycodone were all shown in close agreement with those reported from other studies given intravenous oxycodone in cancer patients [11,13]. The CL value of oxycodone (42.42 L/h) at the 5 mg dose group was also comparable with that (46.8 L/h) in surgical patients [18]. The amount of recovery of unchanged oxycodone from urine in 24 h was approximately 10% which was similar with that (11%) reported previously [8].

It has been known that oxycodone can be metabolized to produce three main metabolites, noroxycodone, oxymorphone and noroxymorphon [9]. Because of the minor amount of metabolites in circulation, few studies have been reported about the pharmacokinetic profile of the three metabolites. In this study, these metabolites were analyzed by a sensitive LC–MS/MS method with a lower LLOQ (0.1 ng/mL) than that (0.25 ng/mL) reported by Neuvonen and Neuvonen [16]. Results showed that the plasma concentrations of the three metabolites increased in proportional to dose. The pharmacokinetics of these metabolites was linear in the dose range of 2.5–10 mg of oxycodone. The mean recovery of these metabolites from urine, as percent of dose, was similar over three doses. Approximately 25% of dose of oxycodone including unchanged parent drug and three free metabolites were recovered. It was supported by previous studies which showed that there were fractions of the four compounds excreted as conjugated glucuronides [8,9].

In addition, there are large inter-individual variations observed in $t_{1/2}$, especially in 2.5 mg dose group. The oxycodone $t_{1/2}$ in the 2.5 mg dose group was 8.93 ± 8.34 h, which was higher than those of the other two groups. It was a result of one subject with $t_{1/2}$ value of 30.87 h. Similarly, noroxycodone $t_{1/2}$ (17.48 ± 17.88 h) in the 2.5 mg

Table 3
Summary of pharmacokinetic parameters for oxycodone and three of its metabolites after intravenous administration of 2.5, 5 and 10 mg of oxycodone in Chinese patients with pain.

Pharmacokinetic parameters	Intravenous administration of oxycodone		
	2.5 mg (n = 9)	5 mg (n = 11)	10 mg (n = 12)
C_{max}, ng/mL			
Oxycodone[a,b,c]	65.69 ± 51.38	147.74 ± 77.31	279.68 ± 158.54
Noroxycodone[a,b,c]	1.68 ± 0.76	3.22 ± 0.94	7.88 ± 1.29
Oxymorphone[c]	–	0.26 ± 0.1 (n = 10)	0.48 ± 0.18 (n = 11)
Noroxymorphone[b,c]	0.37 ± 0.26 (n = 5)	0.60 ± 0.30	1.26 ± 0.53
T_{max}, h			
Oxycodone	0.14 ± 0.33	0.04 ± 0.01	0.05 ± 0.03
Noroxycodone	3.39 ± 2.18	1.15 ± 1.22	1.45 ± 1.39 h
Oxymorphone	–	0.40 ± 0.29 (n = 10)	0.78 ± 1.74 (n = 11)
Noroxymorphone	7.10 ± 7.82 (n = 7)	3.78 ± 3.07	2.16 ± 2.00
AUC_{0-t}, h ng/mL			
Oxycodone[a,b,c]	67.56 ± 22.56	117.29 ± 25.34	227.62 ± 45.16
Noroxycodone	23.04 ± 10.10	40.31 ± 17.09	91.16 ± 16.78
Oxymorphone[c]	–	0.75 ± 0.53 (n = 10)	1.66 ± 1.07 (n = 11)
Noroxymorphone[b,c]	4.92 ± 3.66 (n = 7)	7.34 ± 3.88	17.91 ± 5.70
$AUC_{0-\infty}$, h ng/mL			
Oxycodone[a,b,c]	83.75 ± 54.49	124.59 ± 30.5	231.32 ± 46.51
Noroxycodone[a,b,c]	40.60 ± 28.08	51.08 ± 34.70	102.06 ± 21.49
Oxymorphone[b]	–	2.52 ± 2.15	3.04 ± 1.0
Noxymorphone	9.07 ± 5.79 (n = 5)	10.47 ± 3.25	30.64 ± 32.38
$t_{1/2}$, h			
Oxycodone	8.93 ± 8.34	4.59 ± 0.8	4.17 ± 0.45
Noroxycodone[b]	17.48 ± 17.88	8.08 ± 4.59	6.90 ± 1.24
Oxymorphone	–	7.64 ± 6.29 (n = 10)	6.28 ± 2.31 (n = 9)
Noroxymorphone	13.88 ± 10.35 (n = 5)	11.98 ± 13.22 (n = 10)	13.78 ± 11.44
CL, L/h			
Oxycodone	37.57 ± 15.85	42.42 ± 10.44	44.92 ± 9.4
CL_m, L/h			
Noroxycodone	4.94 ± 2.52	4.97 ± 3.14	6.32 ± 3.26
Oxymorphone	–	0.15 ± 0.09	0.11 ± 0.05 (n = 11)
Noroxymorphone	0.92 ± 0.68	1.29 ± 0.84 (n = 10)	1.33 ± 0.74
V, L/kg			
Oxycodone[b]	6.29 ± 2.75	4.61 ± 0.91	4.34 ± 0.94
Noroxycodone	1.55 ± 1.28	1.25 ± 1.89	1.03 ± 0.52
Oxymorphone	–	0.02 ± 0.02 (n = 10)	0.02 ± 0.01 (n = 9)
Noroxymorphone	0.36 ± 0.23 (n = 5)	0.29 ± 0.19 (n = 10)	0.39 ± 0.29
AUC_{0-t} ratio			
Noroxycodone/oxycodone	0.35 ± 0.14	0.36 ± 0.18	0.42 ± 0.12
Oxymorphone/oxycodone	–	0.007 ± 0.005	0.008 ± 0.005
Noroxymorphone/oxycodone	0.08 ± 0.06	0.06 ± 0.03	0.08 ± 0.02
Excretion in the urine, μg (%)			
Oxycodone	263.91 ± 128.94 (10.56 ± 5.16)	485.23 ± 214.79 (9.70 ± 4.30)	978.18 ± 502.18 (9.78 ± 5.02)
Noroxycodone	332.03 ± 121.78 (13.28 ± 4.87)	588.45 ± 313.87 (11.77 ± 6.28)	1366.56 ± 524.52 (13.67 ± 5.25)
Oxymorphone	6.70 ± 3.89 (0.27 ± 0.16)	18.35 ± 13.54 (0.37 ± 0.27)	(0.23 ± 0.10)
Noroxymorphone	57.14 ± 27.91 (2.29 ± 1.12)	156.31 ± 115.57 (3.13 ± 2.31)	288.48 ± 126.03 (2.88 ± 1.26)

Note: –, the concentration of only one subject could be measured.
[a] Significant difference between IV oxycodone 2.5 mg and 5 mg dose.
[b] Significant difference between IV oxycodone 2.5 mg and 10 mg dose.
[c] Significant difference between IV oxycodone 5 mg and 10 mg dose.

dose group was higher than those of other two groups, which was attributed to significantly high $t_{1/2}$ values of 40.07 h and 55.93 h from two subjects. Oxycodone is mainly eliminated by metabolism, which is believed to occur mainly in liver [12]. However, among the enzymes involving metabolism of oxycodone, CYP3A4 expression exists 50-fold inter-individual difference [4] and CYP2D6 expression is regulated by four different genotypes [22], which maybe result in large variations of $t_{1/2}$ in our study.

The C_{max} value of oxycodone in the 5 mg dose group was higher (147.74 ng/mL) than that (59.5 ng/mL) of reported by Leow et al. [12], which was due to the different method of drug delivery and different time of blood sampling. Leow et al. reported that the whole injection of oxycodone hydrochloride solution completed over 0.5–5 min and blood sampling began at the 2 min after administration. However, in our study, the 10 mL of dissolved oxycodone injection was infused within 2 min and blood samples were collected immediately after dose. The different operation accounted for the difference of C_{max}. Although the C_{max} showed a higher value, AUC of oxycodone in the 5 mg dose group was not different with that of previous report [13]. Furthermore, analysis of safety results showed that most of adverse events (for example, dizziness, nausea, vomiting and drowsiness) occurred in our study was mild to moderate, which was consistent with those reported in other studies [11,17].

In our study, the recruited patients were drawn from applicable people of oxycodone. The participants were all patients with

cancer pain or rheumatic patients with chronic musculoskeletal pain. The number and percentage with musculoskeletal pain and cancer pain in each study group were not very similar, which was a limitation of our study. However, during the study, we found that the treatments were all well tolerated and the incidence of side effects had not significant difference between cancer patients and rheumatic patients. In addition, except for two subjects in 10 mg dose group with moderate nausea and vomiting, others all showed mild side effects. About the pharmacokinetic results, previous researches [23] had indicated that the pharmacokinetics of oxycodone could be influenced by sex, age, liver and renal function, etc. Kirvela et al. [8] reported that the elimination of oxycodone was impaired in uremic patients. Tallgren et al. [24] also reported that oxycodone clearance decreased in severe hepatic failure patients. In our study, all the participants had hepatic function with ALT or AST level less than 2-folds of normal values and had renal function with creatinine level less than 1.25-folds of upper limit of normal value, which indicated that the liver and renal function of our patients could not affect the metabolism and clearance of oxycodone. The consistent results compared to previous research could also support it.

Oxycodone was an analgesic medicine which was widely used in patients with cancer pain or chronic non-cancer pain. Further research of large numbers of patients with cancer pain or chronic non-cancer pain was needed. Our study was the fist research of pharmacokinetic characteristics of oxycodone in Chinese patients. The pharmacokinetics of oxycodone injection in Chinese patients with pain strongly support continued development of oxycodone as an effective analgesic drug in China.

Conflicts of interest

None of the authors have conflicts of interest to disclosure.

Funding

This study was supported by a grant from the Mundipharma Company, supported by the clinical research center of Affiliated Hospital of the Academy of Military Medical Sciences.

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