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Original research article

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

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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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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.