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A disposition kinetic study of Tramadol in bile duct ligated rats in perfused rat liver model

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ABSTRACT

Tramadol hydrochloride is a centrally acting synthetic opioid analgesic drug and is used to treat chronic pain. In this study, the effects of Bile Duct Ligation (BDL) on the pharmacokinetics of tramadol in a liver recirculating perfusion system of male rats were used. Twenty-four Wistar male rats were randomly divided into four groups: control, sham and two weeks BDL and four weeks BDL. Serum levels of liver enzymes were measured before perfusion and the pharmacokinetics of tramadol was evaluated by using liver recirculating perfusion system. Tramadol and metabolites concentrations were determined by HPLC-FL. The sharp increase in liver enzymes level in both BDL groups was observed and significant changes were also observed in liver weight and volume. Tramadol metabolites concentration significantly decreased compared with the control and sham group ($P < 0.05$). The decrease in the hepatic metabolism of tramadol and increase in the half-life of the elimination of tramadol in rats with BDL suggests that personalized treatment and the therapeutic drug monitoring (TDM) data examination are necessary for patients with bile duct diseases and the dose of tramadol should be accordingly adjusted.

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1. Introduction

Tramadol hydrochloride (T) is a synthetic opioid analog of codeine with two chiral centers. This centrally acting analgesic drug, which is used for chronic pain was first introduced in Germany in the late 1970s due to its low respiratory depressant activity [1]. Two mechanisms are recognized for T analgesic activity: binding to μ-opioid receptors and influences the activity of noradrenaline and serotonin reuptake in central nervous system (CNS). The oral absorption of T is rapid with a high volume of distribution [2] but its absolute bioavailability is only 65–70% due to liver first-pass metabolism [3] and plasma protein binding of approximately 20%. Cytochrome P450 enzymes are essential in tramadol metabolism in the liver into three main metabolites, namely, O-desmethyl tramadol (M1), N-desmethyl tramadol (M2) and N, O-di desmethyl tramadol (M5) [4].

Bile Duct Obstruction (BDO) is the disruption of enterohepatic circulation that causes functional and structural changes [5] in liver parenchyma by the intrahepatic and systemic accumulation of bile salts, which leads to progressive fibrogenesis [6]. Hepatic cirrhosis is one of the most common causes of humans morbidity and mortality [5]. BDO occurs by many genetic or acquired disorders of bile formation and its flow: gallstone, the tumor of the bile duct, biliary surgery or pancreatitis, sepsis, coagulopathy, immune depression, hepatic and renal failure [7,8]. Liver dysfunction in BDO decreases the solubilization of lipid-soluble drugs [9] and drug metabolism due to the oxidative stress in patients with BDO. Therefore any disruptions of the liver may influence the blood flow thereby alter T and its metabolites. In spite of rapid oral absorption of Tramadol, its absolute bioavailability is only 65–70% due to hepatic first-pass metabolism [3]. Therefore, this study aimed to evaluate the effects of BDO on the pharmacokinetics and metabolism of T by using isolated perfused rat liver as a model to study drugs hepatic metabolism. Moreover bile duct ligation (BDL) was used as one of the common models to examine BDO and liver cholestasis disease [10,11].

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2. Materials and methods

Tramadol hydrochloride (T), M1, M2 and M5 were purchased from Stolberg, Germany. HPLC-grade acetonitrile (ACN), methanol, Ethyl acetate (AcOEt) and phosphoric acid (85%) were obtained from Merck (Darmstadt, Germany). Other materials were analytical grade and did not need any purification.

2.1. Animal

We used 24 Wistar male rats weighing approximately 200–250 g. They were kept at the temperature of a controlled environment (25 ± 2 °C) with a 12 h light/dark cycle. A standard rat pellet diet and water was provided for the rats. Rats were divided randomly into 4 groups (n = 6): Control (without any surgery kept for 4 weeks), Sham (without BDL surgery kept for 4 weeks), 2 weeks BDL (with BDL surgery kept for 2 weeks after surgery) and 4 weeks BDL (with BDL surgery kept for 4 weeks after surgery). The ethical committee of Tehran University of Medical Sciences has approved the study.

2.2. Liver damage by BDL

We used standard common BDL technique to induce liver damage as described previously [10,11]. Briefly, rats were anesthetized by mixture of ketamine (75 mg/kg) and xylazine (15 mg/kg), then midline of abdomen were cut and the common bile duct was located and ligated with 3-0 nylon suture at both sides of duct (lower down the junction of the hepatic duct and before entry point of the pancreatic duct). After ligation, the bile duct was cut between two points. At the end of the surgery, the abdominal layers were closed and animals were recovered. In the sham group, we have an abdominal incision but without BDL.

2.3. ENZYM analyses

Alanine aminotransferase (ALT/GPT) and aspartate aminotransferase (AST/GOT) were analyzed by using a standard biochemical kit (Pars Azmon, IRAN). Blood samples were collected from each rat. After coagulation at room temperature, the samples were centrifuged at 1800*g* for 15 min to separate serum.

2.4. Liver histological studies

Part of liver tissue from all 4 groups was fixed in 10% buffered formalin. Hepatic tissue was dehydrated and embedded in paraffin. Cross-sections were stained using hematoxylin and eosin (H & E) to evaluate liver histopathologic damages.

2.5. Liver perfusion technique

Rats were anesthetized as previously mentioned. After abdominal incision of the anesthetized rat, the portal vein and superior vena cava were located and cleaned, and then we used intravenous PE-16–18 for cannulating the veins. We injected 500 units of heparin into the inferior vena cava to prevent clotting. The Krebs-Henseleit buffer (118 mm NaCl, 4.5 mm KCl, 2.75 mm $CaCl_2$, 1.19 mm KH_2PO_4, 1.18 mm $MgSO_4$ and 25 mm $NaHCO_3$,) [3] was used as perfusion buffer. The buffer was oxygenated with 95% O_2 and 5% CO_2 buffer pH was 7.4 and the temperature was set to 37.8 °C, and the flow rate was 10 ml/min. The perfusate flow from the superior vena cava lead to perfusion tank (recirculating perfusion) and samples were collected from perfusion tank every 10 min for a period of 180 min for further analysis. The whole volume of the perfusion tank was 200 ml and tramadol concentration in the whole buffer was 500 ng/ml. Buffer pH and temperature as well as flow rate were monitored through the period and remained constant. Liver viability and enzymes activities (AST and ALT) were also continuously controlled and evaluated.

2.6. Hplc-fl

We used a high-performance liquid chromatography system with a low-pressure mixer pump and a fluorescence detector. The ChromGate chromatography software (Knauer, Berlin, Germany) was the main software to process data in this study. We achieved chromatographic separation by a ChromolithTM performance RP-18e 100 mm–4.6 mm column (Merck, Darmstadt, Germany) protected by a ChromolithTM RP-18e 5 mm–4.6 mm Guard Cartridge. In this study, the mobile phase was a mixture of methanol: water (19:81, v/v) adjusted to pH 2.5 by phosphoric acid (final acid concentration = 1.5 mm) at a flow rate of 2 ml/min. The fluorescence excitation and emission wavelengths were set at 200

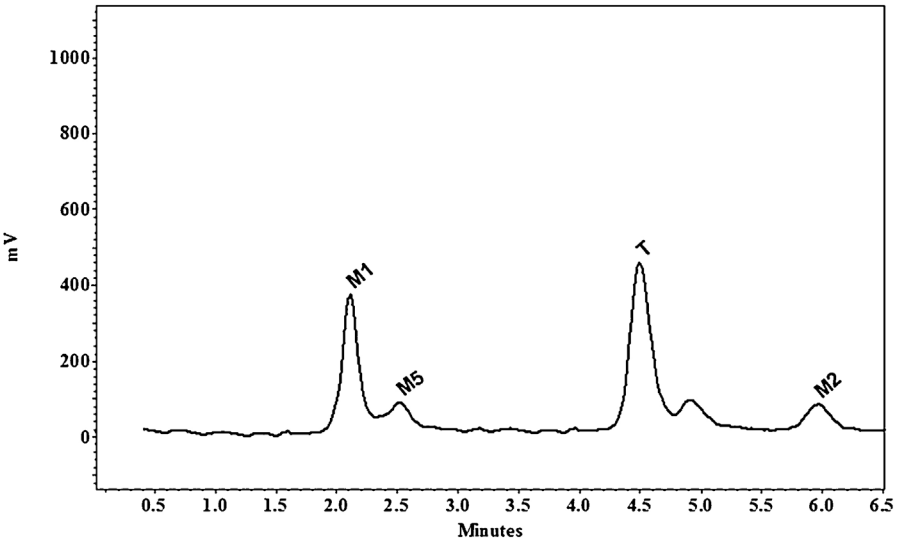

Fig. 1. Example of chromatogram of one perfusate sample after 180 min of recirculation of perfused liver showing Tramadol and its metabolites (M1, M2 and M5).

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