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Original Research Paper

Evaluation of pharmacokinetics underlies the collaborated usage of lamivudine and oxymatrine in beagle dogs

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ABSTRACT

Combinational therapy of lamivudine and oxymatrine has been employed in the battle against hepatitis B virus in clinical setting. However, the pharmacokinetic behavior of the drug or active metabolism in intravenous/oral co-administration regime is poorly investigated. Herein, we evaluated the pharmacokinetic characteristic through a tailor-designed 3 way crossover-Latin square experiment in adult male beagle dogs. Six dogs were randomly treated by intravenous administration of lamivudine (2.5 mg/kg), oxymatrine (15 mg/kg) and combinational dosage, named as intravenous regime. Meanwhile the other six dogs were orally administrated with lamivudine (2.5 mg/kg), oxymatrine (15 mg/kg) and combinational dosage, named as oral regime. The pharmacokinetic feature in simultaneous oral treatment appeared to have no significant difference when compared with individual administration, even including matrine, the active metabolite of oxymatrine. In intravenous regime, the main pharmacokinetic parameters of simultaneous administration were nearly consistent with intravenous regime remedy. The collaborated application of lamivudine and oxymatrine contributed to non-distinctive pharmacokinetic fluctuations of beagle dogs in intravenous/oral regime, compared with individual employment, which established a vital base for the clinical co-administration against hepatitis B. Furthermore, the present study demonstrated that the determination of pharmacokinetics between combinational and individual therapy might assist in the development of drug compatibility in clinical therapy.

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1. Introduction

More than 240 million individuals around the world have suffered from chronic hepatitis B virus (HBV) infection, which is a DNA virus characterized by its reverse transcription for replication in infected hepatocytes [1–4]. At present, the therapy options mainly depend on nucleotide analogues (NA) and interferon alpha (INF-α) [5]. Lamivudine (3TC, Fig. 1A), possessing anti-HBV replicated function, was the first approved oral NA. However, 3TC-resistance phenomena, such as viral drug-resistance and dose-dependent side effects [6], will be likely to emerge in the long-term treatment when using 3TC alone due to the emergence of drug resistance mutations in polymerase protein. To deal with the challenge, co-administrated therapeutic strategy combining 3TC with other antiviral drugs appeared [7–9]. Furthermore, the collaborated employment of lamivudine and oxymatrine could significantly decrease the conversion rate of HBVDNA and hepatitis B e antigen (HBeAg) in patients when compared with mono-therapy of 3TC because of the ability of oxymatrine to inhabit the development of drug resistance to 3TC [6,10–13].

Oxymatrine (OM, Fig. 1B) is a major quinolizidine alkaloid from the Chinese herb *Sophora alopecuraides L.*, *Sophora subprostrata* and *Sophora flavescens Ait.*, and has been extensively used as liver protecting drugs in the treatment of liver ailments in traditional Chinese medicines (TCM) [14]. OM and its active metabolite matrine (M, Fig. 1C) have been proven to have an active antiviral effect on HBV infection in the clinical trials [6,8,11,15,16]. And Xiaoyan Cui reported the superiority of the combination of 3TC with oxymatrine or matrine over 3TC alone [6].

Although the single use of 3TC to treat HBV has largely been replaced by more effective combination with OM, which has been demonstrated previously in the literature, the impact of combination therapy on the pharmacokinetics of each drug or its active metabolite is largely unknown [6]. Herein, the present study is carried out to investigate the effects of OM on the pharmacokinetics of 3TC and to characterize the pharmacokinetic behavior of OM and 3TC during co-administration to beagle dogs following intravenous or oral administration. Whether or not there are significant pharmacokinetic interactions, the results of which will assist in the development of this two-drug combination in clinical therapy strategy.

2. Materials and methods

2.1. Chemicals

3TC (content >98.5%) was purchased from Hefei Scenery Chemical Co., Ltd. (Hefei, Anhui, China). Standard OM, M and famotidine (internal standard) were supplied by the National Institute for the Control of Pharmaceutical and Biological Products (Beijing, China). Bulk OM (content >98.5%) was purchased from Ningxia Bo-er-tai-li Pharmaceutical Co. Ltd. (Yinchuan, Ningxia, China). Acetonitrile was of HPLC grade and other chemicals were of analytical grade.

2.2. Animals

Twelve healthy adult male beagle dogs (Laboratory Animal Center of Shenyang Pharmaceutical University, Shenyang, Liaoning, China) weighing 10 ± 1.3 kg (mean ± standard error) were used for the pharmacokinetic study. The animal experimental protocols described below were approved by the Animal Care and Use Committee at Shenyang Pharmaceutical University.

2.3. Pharmacokinetic experiments

A randomized 3-way crossover-Latin square experiment with a washout period of 1 week was designed. Dogs ($n = 6$) were randomly assigned to groups to characterize the pharmacokinetics and interaction of 3TC (2.5 mg/kg) and OM (15 mg/kg) given intravenously alone and in combination. Another six dogs were used to characterize the pharmacokinetics and interaction of 3TC (5.0 mg/kg) and OM (30 mg/kg) given orally alone and in combination. The dogs were housed in standard stainless-steel cages under a 12 h light/dark cycle with access to water and standard laboratory diet. The drugs were administered to all dogs following an overnight fast, and access to food was restored 4 h after dosing. In the intravenous administration study, blood samples were collected prior to drug administration and at 2, 5, 10, 15, 30, 45, 60, 90, 120, 150, 180, 240, 360 and 480 min after dosing through an intravenous catheter placed in the opposite foreleg vein. In the oral administration study, blood samples were collected prior to drug administration and at 10, 20, 30, 45, 60, 90, 120, 150, 180, 240, 300, 360, 540 and 720 min after dosing through an intrave-

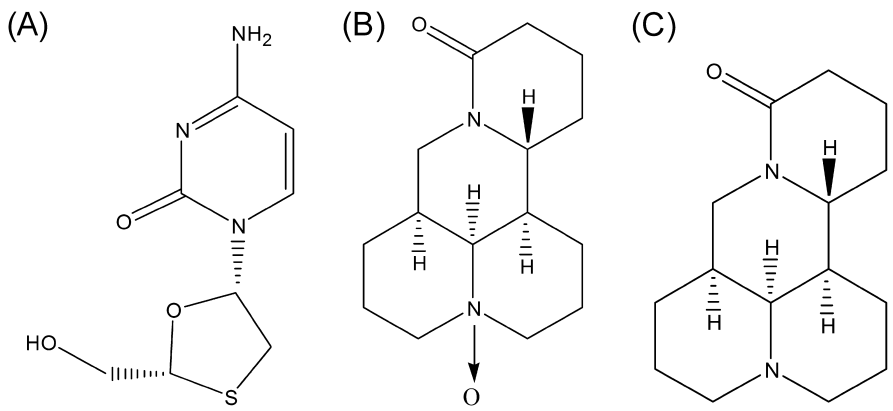

Fig. 1 – Structures of 3TC, OM and M (A-3TC; B-OM; C-M).