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Distribution of liposomal breviscapine in brain following intravenous injection in rats

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Abstract

Aim: To investigate distribution of breviscapine in brain after intravenous (i.v.) injection of liposomes.
Methods: Breviscapine liposomes were prepared by rotary evaporation–sonication method. Particle size, encapsulation efficiency and stability of liposomes were respectively examined. In vitro drug release was investigated in 0.9% sodium chloride at 37 °C. Rats were divided into two groups. Liposomes were given to one group and commercial injection (*Injectio Breviscapine*) was given to the other at a single dose of 28.1 mg kg^{-1} i.v., respectively. Scutellarin in rat brain at different sampling time was determined by RP-HPLC. The brain concentration–time curves of breviscapine liposomes and commercial injection were constructed and pharmacokinetic parameters were calculated and compared by statistic analysis.
Results: The average liposome diameter was 735 ± 59 nm and encapsulation efficiency was 85.1 ± 2.3%. The average accumulative release percentage of breviscapine liposomes in 0.9% sodium chloride was less than 30% within 24 h. The mean concentration–time curves of breviscapine liposomes and commercial injection were both fitted to one-compartment model. There are significant difference of parameter $T_{1/2}$ and AUC_{0-360} between liposome and commercial injection ($p < 0.05$). $T_{1/2}$ of breviscapine liposomes and commercial injection were 23.13 ± 7.71 and 6.27 ± 1.84 min, respectively. The brain AUC ratio of breviscapine liposomes to commercial injection was 443.4 ± 92.3%.
Conclusion: Compared with the commercial injection, liposomes delivered more drugs into the brain and have longer elimination time.

Keywords: Breviscapine; Scutellarin; Liposomes; Pharmacokinetics; RP-HPLC

1. Introduction

Breviscapine is the flavonoid constituents extracted from Chinese herb *Erigerin breviscapus* (Vant.) Hand-Mazz. It contains mainly scutellarin and a small quantity of apigenin-7-*O*-glueuronide. Scutellarin is the primary active ingredient of breviscapine (Zhang et

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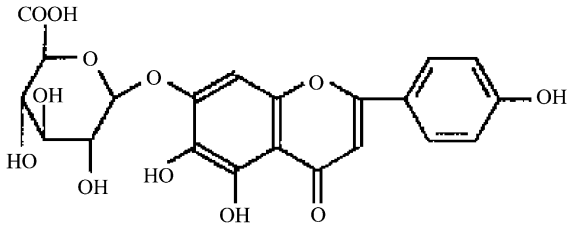

Fig. 1. Structure of scutellarin.

al., 2000). The structure of scutellarin was shown in Fig. 1. It is a sort of flavone glycoside. In China, the preparations of breviscapine (*Injectio Breviscapine* and *Breviscapine Tablets*) are extensively used for the treatment of cerebrovascular diseases such as paralysis caused by cerebral infarction, hypertension and chronic arachnoiditis along with their sequelae (Zhang et al., 2002). It has been reported that breviscapine possesses anticoagulation effect (Zhou et al., 1992) and can protect against cerebral ischemia-reperfusion injury by many pathways of action (Shi et al., 1998; Shuai and Dong, 1998). In recent years, many studies have provided evidences for the neuroprotective effects of scutellarin. It has been reported scutellarin exerts a potent protective effect against oxidative damage in synaptosomes induced by superoxide (Liu et al., 2003a). The neuroprotective properties of scutellarin have been explored at the cellular level (Hao and Liu, 2004).

However, it has been reported that the absolute bioavailability of breviscapine oral preparations was only $0.4 \pm 0.19\%$ (Ge et al., 2003). The pharmacokinetics of breviscapine at a single intravenous dose to rabbits and dogs have also been studied (Li et al., 2003; Liu et al., 2003b). It was shown that scutellarin eliminated rapidly in the blood and the plasma concentration–time curve was fitted to a three-compartment model, which indicated the fast distribution of scutellarin in vivo. The result of biodistribution study of breviscapine in mice after intravenous injection showed that most of ^{3}H-scutellarin accumulated in the cholecyst, intestine and dejecta within 1 h, and 41.2% of ^{3}H-scutellarin was found in the excrement and urine within 24 h (Cai, 1981).

Liposomes have long been used as drug delivery system (DDS) to realize long-circulation and target-delivery of drugs (Aquilur et al., 1986). In order to prolong the residence of breviscapine in blood and deliver more breviscapine into brain, breviscapine liposomes were prepared and the pharmacokinetic behavior of breviscapine liposomes and commercial injection (*I. Breviscapine*) in rat brain were compared.

2. Experimental

2.1. Materials

Breviscapine was purchased from Yunnan Plant Pharmaceutical Industry Ltd. (Yunnan, China). Soybean phosphatidylcholine was purchased from Shanghai Taiwei Pharmaceutial Industry Ltd. (Shanghai, China, PC > 92%). Cholesterol was obtained from Shanghai Chemical Reagent Co. (Shanghai, China). *I. Breviscapine*, an injection solution of scutellarin (20 mg/5 mL), was manufactured by Dilong Pharmacy Ltd. (Heilongjiang, China). Scutellarin (purity 96.4%) and rutin (internal standard, IS) were purchased from National Institute for Control of Pharmaceutical and Biological Products (Beijing, China). Methanol and acetonitrile were of HPLC-grade. NaH_2PO_4 and other chemicals used were of analytical grade. Water was double distilled.

2.2. Animals

Wistar rats (200 ± 20 g body weight) were provided by the Animal Center of China Pharmaceutical University).

2.3. Chromatographic conditions

The concentration of scutellarin was determined by HPLC. The HPLC system was consisted of two pumps (HP1100, Agilent, USA), a Diamonsil C18 column (4.6 mm × 250 mm, 5 μm, Dikma, Beijing, China) with a Shim-park C18 precolumn (4 mm × 3.0 mm, 5 μm, Simadzu, Tokyo, Japan) maintained at 35 °C, an UV detector (HP1100, Agilent, USA) at 335 nm and an autosampler (HP1100, Agilent, USA). The HP1100 ChemStation software was applied on the HPLC system. The mobile phase consisted of methanol–acetonitrile–0.5%phosphoric acid (35:10:65 v/v/v) was delivered at a flow rate of 1.0 mL min^{-1}.