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Technical note

High-performance liquid chromatographic determination of evodiamine in rat plasma: application to pharmacokinetic studies

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Abstract

A previously published simple and sensitive high-performance liquid chromatographic method for determination and identification of rutaecarpine in rat plasma was used for evodiamine determination. However, the ultraviolet detection was not 344 nm, but 227 nm. The method was applied to a pharmacokinetic study of evodiamine in rats after 2 mg/kg intravenous administration. A biphasic phenomenon with a rapid distribution followed by a slower elimination phase was observed from the plasma concentration–time curve. Compartmental analysis yielded a two-compartment model.

1. Introduction

Evodiamine is one of the major bioactive components of a Chinese herbal drug named Wu-Chu-Yu, the dried unripened fruit of *Evodia rutaecarpa* (Juss.) Benth. [1]. Wu-Chu-Yu has been used in the traditional Chinese medicine for the treatment of abdominal pain, gastrointestinal disorders, headache, dysentery, postpartum haemorrhage and amenorrhea [2]. The pharmacological effects of its bioactive components, dehydroevodiamine [1,3–5], evodiamine [6] and the assay methods of dehydroevodiamine [1,7] and rutaecarpine [8] have been previously reported. A [^{3}H]evodiamine determination method has been reported [9]. However, the isotope method is uncommon for other laboratories. Thus, the HPLC method coupled with ultraviolet or photodiode-array detection of rutaecarpine was used for the detection of evodiamine in rat plasma and was also applied in a pharmacokinetic study.

2. Experimental

Most chemicals, apparatus, chromatographic conditions, rat blood sampling, plasma treatment and pharmacokinetic data analysis used in the present study were the same as reported previously [8], except that evodiamine was used (Fig. 1) instead of rutaecarpine, and the detection

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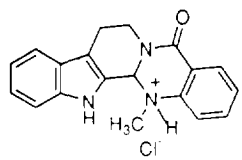

Fig. 1. Structure of evodiamine HCl.

wavelength of evodiamine was 227 nm. The internal standard, paeonol [10] was extracted from *Paionia suffruticosa* Andr.

3. Results and discussion

Under the conditions described above, the retention times of paeonol and evodiamine were found to be 5.2 and 6.5 min, respectively (Fig. 2). Further, the spectrum obtained in the mobile phase showed absorption maxima at 212 and 275 nm for paeonol and at 227 nm for evodiamine. The detection limit for evodiamine, at a signal-to-noise ratio of 4, was 0.01 μg/ml in rat plasma. The recoveries of evodiamine from rat plasma were found to be 95.33, 92.12, and 93.86% for concentrations of 0.5, 1, and 2 μg/ml, respectively.

The intra-day C.V.s for evodiamine at concentrations of 0.2, 1, and 2 μg/ml were 7.51, 6.02, and 2.98%, respectively, and the inter-day C.V.s for evodiamine at the same concentrations were 5.69, 4.69, and 2.32%, respectively.

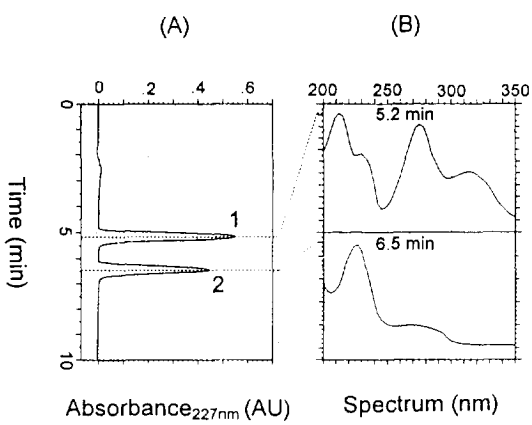

Fig. 2. Peaks (A) and UV spectra (B) of authentic paeonol and evodiamine, measured by Waters photodiode-array detector (Model 990). 1 = Paeonol. 2 = evodiamine.

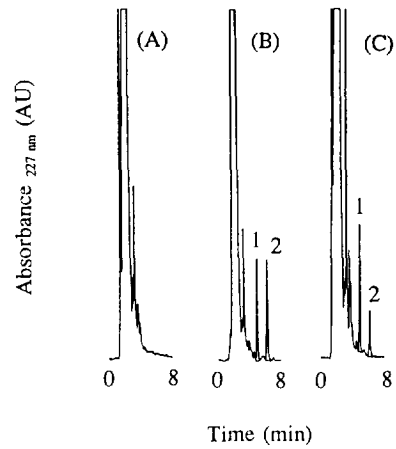

Fig. 3. Chromatograms of evodiamine in rat plasma: (A) blank plasma; (B) blank plasma spiked with evodiamine (0.5 μg/ml) and internal standard (paeonol); (C) plasma sample 20 min after a 2 mg/kg intravenous dose of evodiamine (0.21 μg/ml). 1 = Paeonol, 2 = evodiamine.

Fig. 3A shows the chromatogram of blank rat plasma. No discernible peaks were observed within the time frame in which evodiamine and paeonol were detected. Fig. 3B shows the chromatogram of rat plasma spiked with evodiamine (0.5 μg/ml) and paeonol. Fig. 3C shows the chromatogram of evodiamine (0.21 μg/ml), a sample obtained 20 min after intravenous administration of evodiamine (2 mg/kg) to a rat.

The curve of the concentration in plasma versus the time after intravenous administration of evodiamine (2 mg/kg) is shown in Fig. 4.

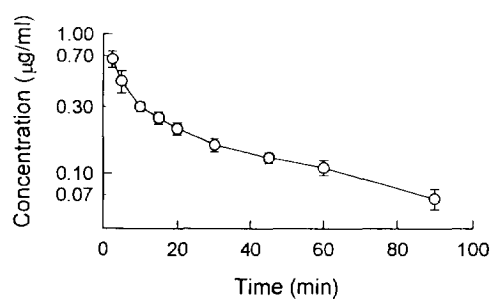

Fig. 4. Plot of concentration in plasma versus time after intravenous administration of evodiamine in rats at a dose of 2 mg/kg.

Analysis of data after intravenous bolus injection of evodiamine at 2 mg/kg yielded the equation: $C = 1.37\ e^{-0.37t} + 0.28\ e^{-0.02t}$. The pharmacokinetic parameters, apparent total body clearance (Cl), elimination half-life ($t_{1/2,\beta}$), apparent volume of distribution (Vol) and area under the curve (AUC), as derived from these data and calculated by PCNONLIN (SCI software, Lexington, KY, USA), are shown in Table 1.

In conclusion, the UV spectrum identification, plasma sample extraction and chromatographic procedures described in this study allow the quantification of evodiamine in rat plasma. The pharmacokinetic study of evodiamine (2 mg/kg, i.v.) was characterized by the two-compartment model.

Table 1
Pharmacokinetic parameters of evodiamine in rats after intravenous administration of 2 mg/kg

Parameter (units)	Estimate
$t_{1/2,\beta}$ (min)	44.56 ± 5.80
Cl (ml min^{-1} kg^{-1})	102.71 ± 9.64
Vol (ml kg^{-1})	2222.08 ± 729.12
AUC (μg min ml^{-1})	20.99 ± 2.78

Data are expressed as mean ± S.E.M. ($n = 7$).

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