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Determination and pharmacokinetics of ergometrine maleate in rabbit blood with on line microdialysis sampling and fluorescence detection

Yi Lv[1], Zhujun Zhang*, Zhengjun Gong, Yufei Hu, Deyong He

Institute of Analytical Science, Department of Chemistry, Southwest Normal University, Beibei, Chongqing 400715, PR China

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Abstract

The study describes a flow injection on-line microdialysis system for in vivo monitoring of ergometrine maleate in rabbit blood with fluorescence detection. A flow-through microdialysis probe was used for intravenous sampling by pumping of the blood from the tested rabbit through the flow-through microdialysis probe located outside the living system at a flow rate of 15 μl min^{-1}. The perfusion rate is 5 μl min^{-1}. The ergometrine maleate in the dialysate was detected on-line with a flow injection fluorescence system after the ergometrine maleate administration (0.2 mg kg^{-1}, i.v.). The dialysate sample volume was about 15 μl. The system was linearly related to the concentration of ergometrine maleate in the range 1–140 ng ml^{-1} ($r = 0.9989$) with a detection limit 0.3 ng ml^{-1} (3σ). The pharmacokinetic parameters of ergometrine maleate were calculated utilizing the pharmacokinetic software 'NDST-21' by a one-compartmental open model.

Keywords: Ergometrine maleate; Microdialysis; In vivo; Fluorescence; Pharmacokinetics

1. Introduction

In recent years, microdialysis sampling has become a well-known technique for in vivo monitoring of biochemical constitutes in the extracellular fluid (ECF) of virtually any tissue, organ or biological fluid [1]. While microdialysis sampling was originally developed mainly to monitor neurotransmitter release in the brain [2], over the past decade the technique has been employed extensively for in vivo analysis at other sites of living systems, such as muscle [3], liver [4,5], bile [6], skin [7,8], tumor [9], blood and brain [10–13]. Furthermore, the application of microdialysis sampling has been extended to many other fields including toxicology [4], bioprocess monitoring [14] and pharmacokinetics [11–13].

The flow-through microdialysis probe, originally introduced by Fang et al. [15], enables the monitoring of the concentration of glucose in the blood of rabbit by pumping of the blood from the tested rabbit through the microdialysis probe located outside the living system. A diagram of the flow-through microdialyzer is shown in Fig. 2. If the microdialysis probe is implanted in a blood stream, the disadvantages of microdialysis system are obvious. The variations in blood flow always somewhat affect analyte transfer through dialysis membranes [16], furthermore, irreproducible partial obstruction of membrane surface of a dialysis probe by the vein walls during implantation and/or during the monitoring processes cannot be completely avoided [15]. However, those disadvantages can be avoided by the flow-through microdialysis probe. In recent years, flow-injection analysis (FIA) is a widely used methodology to perform the automation of analytical progress in many fields so several works dealing with FIA combined with microdialysis have appeared in the literatures [15,17–19].

Ergometrine maleate ((8s)-9,10-didehydro-*N*-[(s)-2-hydroxy-1-methylethyl]-6-methylergoline-8-carboxamide mon-

* Corresponding author. Tel.: +86 23 68253863; fax: +86 23 68253863.
E-mail addresses: lvymail@yahoo.com.cn (Y. Lv), zzj18@hotmail.com (Z. Zhang).
[1] Present address: Analysis Center, Department of Chemistry, Tsinghua University, Beijing 100084, PR China.

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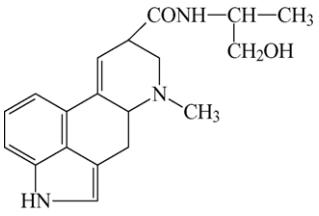

Fig. 1. Structure of ergometrine.

omaleate) is a naturally occurring amino ergot alkaloid, used as an orally active obstetric drug and it has a direct stimulating action on the vascular smooth muscle. Several methods have been reported for the determination of ergometrine maleate such as HPLC [20], spectrophotometry [21], immunoassay [22,23], amperometry [24], and chemiluminescence [25]. Fluorescent detection is widely used in quantitative analysis because of its great sensitivity and good selectivity as well as its relatively low cost. Ergometrine (Fig. 1) has a property of fluorescence [26], however, few reports describe the microdialysis sampling method coupled with fluorescent detection for determination of ergometrine maleate.

Therefore, in the present study we use an in vivo on-line microdialysis sampling method coupled with flow-injection analysis fluorescence detection for the measurement of ergometrine maleate in the rabbit blood. Furthermore, the pharmacokinetic analysis of results were obtained utilizing software 'NDST-21'.

2. Experimental

2.1. Reagents and standard solutions

All chemicals were of analytical reagent grade, and doubly distilled water was used throughout. The Ringer's solution containing 148 mM NaCl, 4.0 mM KCl and 2.3 mM $CaCl_2$ used as perfusion medium was prepared by dissolving 8.65 g of NaCl and 0.30 g of KCl and 0.26 g of $CaCl_2$ in 1 l of water. Ergometrine maleate was purchased from Harvest Pharmaceutical Corporation (Shanghai, China). Aqueous ergometrine maleate standards were prepared by sequential dilution of a stock solution containing 10 μg ml^{-1} ergometrine maleate with perfusion solution.

2.2. Instrumentation

Microdialysis sampling was performed using a KH-1 microdialysis syringe pump controller (Institute of Chemistry Academy of Sciences, China) coupled to a flow-through microdialysis probe. A microdialysis syringe pump (1000 μl volume) was used for delivery of perfusate. A variable peristaltic pump (Xi'an Ruimai Instrumental Factory, Xi'an, China) was used for pumping the blood from the tested rabbit. PTFE tubing of (0.25 mm i.d., 0.8 mm o.d.) was used for all connections. The microdialysis manifold is shown in Fig. 2.

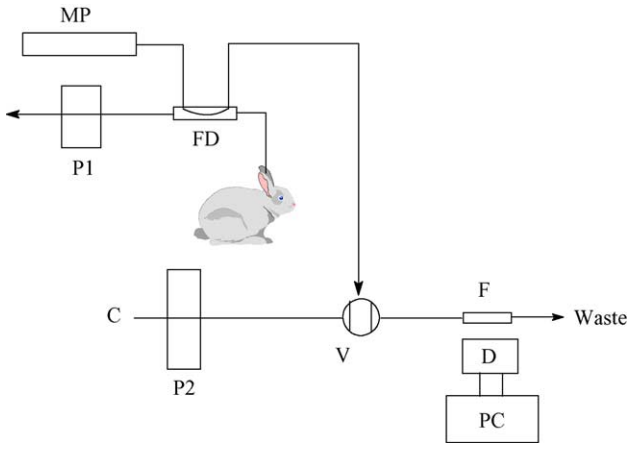

Fig. 2. Schematic diagram of flow system for in vivo on-line determination of ergometrine maleate in awake rabbit by microdialysis sampling. C: carrier flow (H_2O); MP: micropump and its controller system; FD: flow-through microdialysis probe; P1: variable-speed peristaltic pump (μl min^{-1}); P2: three channel peristaltic pump (ml min^{-1}); V: valve; F: flow cell; D: detector of F-4500 fluorescence spectrophotometer; PC: personal computer.

Fluorescence intensity was measured on the Hitachi F-4500 fluorescence spectrophotometer (Hitachi, Japan) equipped with a xenon-pulsed (10 s half-width, 50 Hz) excitation source. The excitation and emission slits were set at 2.5 and 5.0 nm, respectively. A conventional Perkin-Emer L2251247 flow-cell (25 μl volume) was used. A three channel peristaltic pump (Wenzhou, China) and an eight-channel injector valve (Wenzhou, China) were used to construct the FI system.

2.3. Fabrication of flow-through microdialyser

The preparation procedure of the flow-through microdialyzer was similar to that proposed by Fang et al. [15]. Two apertures (i.d. 0.6 mm) with a distance of 3.8 mm were made by needle through the wall of a micro-Line tubing (0.8 mm i.d., 1.2 mm o.d., 6.5 mm long, Thermoplastics, Chengdu Medical Appliance Corporation, China). A linear microdialysis probe (MF-7051) from Bioanalytical System (BAS) (West Lafayette, IN, USA) was then threaded into the micro-line tubing from one aperture and out from another aperture, and ensured that the dialysis membrane of probe completely be in the micro-line tubing. The connections between the linear microdialysis probe and the micro-line tubing were sealed with epoxy.

2.4. In vitro experiments

In these experiments, aqueous standard solutions were used instead of real samples from tested rabbit. The calibration of the measurement was performed by a flow-through microdialyzer in the Ringer's solution with variable concentrations of ergometrine maleate. The perfusion rate was used at 5 μl min^{-1}, and the sample flow rate was 15 μl min^{-1}. A different concentration of ergometrine maleate solution was