Journal of Chromatography B, 937 (2013) 97–102

Contents lists available at ScienceDirect

Journal of Chromatography B

journal homepage: www.elsevier.com/locate/chromb

Determination of Prostaglandin E_1 in dog plasma using liquid chromatography–tandem mass spectrometry and its application to a pharmacokinetic study

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ARTICLE INFO

Article history:
Received 21 June 2013
Received in revised form 8 August 2013
Accepted 13 August 2013
Available online 23 August 2013

Keywords:
Prostaglandin E_1
LC–MS/MS
Pharmacokinetics
Beagle dog
Plasma

ABSTRACT

The determination of Prostaglandin (PG) E_1 in plasma is challenged by its low concentration (pg/mL) and endogenous interference. An LC–MS/MS method for the determination of PGE_1 in dog plasma has been developed and validated. Plasma being sampled at 4 °C and treated with indomethacin effectively inhibited interferents synthesized post-sampling. Samples were subjected to one-step extraction and separated by reversed phase HPLC with a short cycle time of 3 min. An LLOQ of 10 pg/mL was achieved with 500 μl plasma. The method was applied to a pharmacokinetic study in beagle dogs involving an intravenous infusion of 3.2 μg/kg PGE_1. The half-life was recovered at 7 min. The simple, sensitive and rapid method was suitable to be applied to pharmacokinetic studies of PGE_1 at clinically relevant doses.

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1. Introduction

Prostaglandin (PG) E_1 (Fig. 1), also known as alprostadil, is a vasodilator widely used for the treatment of ischemic peripheral vascular disease [1–4]. It exerts multiple effects on peripheral vascular system, including increase of peripheral blood flow [5] and viscosity [6], modulation of fibrinolytic system [7], and inhibition of platelet aggregation [8]. The drug is also administrated intraurethrally and intracavernosally as a second-line therapy for erectile dysfunction [9]. It has been known that PGE_1 is inactivated rapidly by lung [10,11]. Based on its short half-life, the drug is recommended to be administrated by intravenous infusion to maintain plasma PGE_1 concentrations and thus prolong its action for the treatment of peripheral arterial occlusive disease [12].

Recently, prolonged release preparations of PGE_1 were developed in order to expand its administration routes and facilitate clinical application. However, it was a challenge to evaluate these preparations by pharmacokinetic studies due to the difficulty to determine PGE_1 in plasma as well as in other biological samples. Furthermore, although the drug has been applied in clinical practice for decades, to date there are very few reports on its pharmacokinetics. The determination of plasma PGE_1 is not only challenged by its low levels (pg/mL) following a dose in microgram order [13], but also challenged by the endogenous interferents. Endogenous PGE_1 at normal physiological level is very low in plasma, such as 1–3 pg/mL in human plasma [14], and therefore does not significantly interference the determination of exogenous PGE_1. However, great amounts of interferents, probably PGE_1 and other PGs, could be biosynthesized from the phospholipids released from cell membrane residues remaining in plasma. The occurrence of post-sampling interference at high levels made it impossible to quantitation exogenous PGE_1 in low pg/mL order.

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http://dx.doi.org/10.1016/j.jchromb.2013.08.021

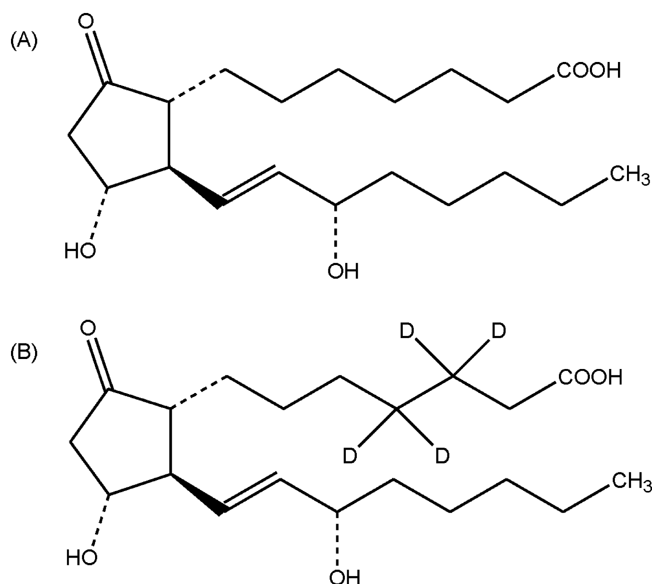

Fig. 1. Prostaglandin E_1 (A) and internal standard, PGE1-d4 (B).

Several methods have been reported concerned with the determination of PGE_1 in biological matrix. Schweer et al. [14] and Hammes et al. [15] reported gas chromatography-tandem mass spectrometry (GC-MS/MS) methods for the determination of PGE_1 in human plasma, with a lower limit of detection (LLOD) of 1 pg/mL and a lower limit of quantitation (LLOQ) of 2 pg/mL, respectively. Although both of the methods provided high sensitivity, they suffered from time-consuming sample preparation procedure of three step derivatization. High performance liquid chromatography (HPLC) based methods were developed by Hotter et al. [16] and Tsutsumiuchi et al. [17] with LLOQs of 3.9 pg/mL and 23 pg/mL, respectively. Expect for analytical run time (30 min), long time was consumed on either radioimmunoassay (24 h) or derivatization (1 h). None of the methods discussed above was suitable to be applied to pharmacokinetic studies based on their low throughputs, e.g. only 24 samples could be prepared per day in the GC-MS/MS method with LLOQ of 2 pg/mL [15]. Rapid and simple LC–MS methods were provided by Abián et al. [18] and Lee et al. [19] with LLOQs of 50 ng/mL–20 μg/mL. Lin et al. reported an ultra-high performance liquid chromatography–tandem mass spectrometry (UPLC–MS/MS) method for the determination of PGE_1 in plasma and the method was applied to a pharmacokinetic study involving an intravenous injection of PGE_1 [20]. The method was rapid and simple with one-step sample preparation and run time of 2 min. However, it suffered from an LLOQ of 400 pg/mL, which led to a non-clinically-relevant dose of 50 μg/kg PGE_1 for the pharmacokinetic study in rats.

In order to solve these problems, a liquid chromatography–tandem mass spectrometric (LC–MS/MS) method for the determination of PGE_1 in dog plasma was developed and it has been successfully applied to a pharmacokinetic study in beagle dogs involving an intravenous infusion of PGE_1 at a therapeutically relevant dose of 3.2 μg/kg. The method involved one-step sample preparation, a short analytical time (cycle time 3 min) and high sensitivity (LLOQ 10 pg/mL). Indomethacin was added to plasma to inhibit post-sampling synthesis of endogenous interferences and low baselines were obtained. The sensitivity of this method (LLOQ 10 pg/mL using 0.5 mL plasma) was comparable with the GC–MS/MS method with an LLOQ of 2 pg/mL using 2 mL plasma, but the former method was much more simple and rapid. This method is being validated with human plasma and will be applied to a phase I clinical study for PGE_1 micelles. An LLOQ of 1 pg/mL has been achieved using 2 mL human plasma.

2. Experimental

2.1. Chemicals and reagents

Prostaglandin E_1 (97.2% purity) and indomethacin (98% purity) were provided by Jilin Yinglian Biopharmaceutical Co., Ltd., (Changchun, PR China). PGE_1-d4 (9-oxo-11α, 15S-dihydroxy-prost-13E-en-1-oic-3,3,4,4-d4 acid) (99% purity) was purchased from Amyjet Scientific Inc. (Wuhan, PR China). Methanol and acetonitrile were HPLC grade and obtained from Fisher Scientific (Fair Lawn, NJ, USA). Ultra-high purity water, prepared using the Milli-Q system, was used through-out the study. All other chemicals were analytical grade and used without further purification. Alprostadil injection (Lot No. 2088S, 2 mL: 10 μg) was purchased from Beijing Tide Pharmaceutical Co., Ltd., (Beijing, PR China).

2.2. LC–MS/MS conditions

Chromatography was performed using an Agilent 1100 HPLC system (Agilent Technologies, CA, USA) equipped with an Agilent Zorbax Eclipse XDB C18 column (150 mm × 4.6 mm, 5 μm) maintained at 30 °C. The mobile phase consisted of acetonitrile-0.5% formic acid in water (50:50, v/v) delivered at a flow rate of 1 mL/min. Mass spectrometric detection employed an API 4000 mass spectrometer (AB Sciex, Ont., Canada) equipped with an electrospray ionization (ESI) source operated in the negative ion mode. The curtain gas, Gas 1 and Gas 2 were nitrogen set at 20, 60, and 60 psi, respectively. The ion spray voltage was adjusted to −4500 V and the source temperature was set at 500 °C. Detection was by multiple reaction monitoring (MRM) at unit resolution for Q1 and unit resolution for Q3 with a dwell time of 200 ms per channel. Transitions of $[M-H]^-$ ions for multiple reaction monitoring (MRM) were at m/z 353.4 → 317.3 and 353.4 → 235.0 for PGE_1 and m/z 357.2 → 321.1 for IS. Declustering potential and collision energy were −55 V and −80 eV for PGE_1 and IS. Mass spectrometric parameters were tuned to maximize the response of the precursor/product ion combinations. Data acquisition and integration were controlled by Applied Biosystems Analyst version 1.3 software.

2.3. Preparation of calibration standards and QC samples

A stock solution of PGE_1 (1 mg/mL) was prepared in methanol. Calibration standards of PGE_1 were prepared by diluting the stock solutions with blank dog plasma (prepared by separating plasma at 4 °C and transferring 1.2 mL plasma to a tube coated with 6 μg indomethacin, see Section 2.6) to concentrations of 10, 30, 100, 300, 1000 and 3000 pg/mL. Quality control (QC) solutions were prepared independently at concentrations of 30, 300 and 2400 pg/mL in the same way. A stock solution (4 μg/mL) of the internal standard (IS), PGE_1-d4 in methanol was diluted in methanol-water (50:50, v/v) to give a 500 pg/mL working PGE1-d4 solution. All solutions were stored at 4 °C.

2.4. Sample preparation

To 500 μL plasma or calibration standard or QC sample in a glass tube, 100 μL 50% formic acid and 100 μL IS working solution were added. The mixture was then shaken with 3 mL diethyl ether-dichloromethane (3:2, v/v), centrifuged for 5 min at 3500 × g and the organic layer transferred to another glass tube and evaporated to dryness at 40 °C under nitrogen. The residue was reconstituted in

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