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Dose proportional pharmacokinetics of alprostadil (prostaglandin E_1) in healthy volunteers following intravenous infusion

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Prostaglandin E_1 (PGE_1) (30, 60, 120 μg) was administered by intravenous infusion over a 120 min period in an open, three way randomized, cross-over study to 12 healthy male volunteers. For the evaluation of PGE_1, PGE_0 and 15-keto-PGE_0, blood samples were drawn prior to, during and after the infusion. Analytical measurements were performed by gas chromatography/negative ion chemical ionization triple stage quadruple mass spectrometry, a highly specific and sensitive GC/MS/MS-method. During intravenous infusion of 30, 60 and 120 μg PGE_1, endogenous plasma PGE_1 concentrations increased from 1.7 ± 0.8 to 4.2 ± 1.1, 6.7 ± 1.0 and 11.0 ± 1.9 pg ml^{-1} respectively. PGE_0 plasma concentrations increased from endogenous levels of 1.3 ± 1.0 pg ml^{-1} to 7.6 ± 2.1, 14.1 ± 3.7 and 28.0 ± 3.0 pg ml^{-1} respectively, whilst 15-keto-PGE_0 plasma concentrations increased from endogenous levels of 10.2 ± 13.9 pg ml^{-1} to 99.3 ± 27.9, 190.4 ± 52.5 and 357.2 ± 72.6 pg ml^{-1} respectively. Within the dose range of 30–120 μg PGE_1 2 h^{-1} there was a linear increase of C_{max} and AUC with the dose. The results of the analysis of variance after baseline and dose-correction show a 90% confidence interval in the bioequivalence acceptance range of 80 to 125%.

Keywords prostaglandin E_1 dose proportional pharmacokinetics human volunteers infusion metabolites

Introduction

Prostaglandin E_1 (PGE_1; alprostadil; Prostavasin®) has been demonstrated to inhibit platelet aggregation [2, 3] and to induce vasodilatation [4]. Based on these properties, the compound has been administered for the treatment of arterial occlusive disease stages III or IV, based on the classification described by Fontaine [4, 5].

PGE_1 is bound to α-cyclodextrin (α-CD), a cyclic glucose oligomer and this enhances chemical stability and solubility in water [8]. The solid complex rapidly goes into solution, where it undergoes instantaneous dissociation [9]. PGE_1 will then be found in the free form, without α-cyclodextrin-complexation, and the whole dose of PGE_1 is bioavailable.

We have previously studied the pharmacokinetics of PGE_1, PGE_0 and 15-keto-PGE_0 after i.v. administration of a single dose of PGE_1 to healthy volunteers [6, 7]. The aim of the present study was to investigate the pharmacokinetics of PGE_1 and its main metabolites in healthy volunteers following intravenous administration of escalating doses of PGE_1.

Methods

In a three-way cross over design, 12 healthy male volunteers aged 20 to 35 received PGE_1 (Prostavasin®, Schwarz Pharma AG) in a single i.v. infusion of 30, 60 and 120 μg PGE_1 (each dose dissolved in 100 ml of physiological NaCl-solution) over a 2 h period. Informed consent was obtained from all volunteers. The study protocol was approved by the ethics committees institutional review board (IRB) and Bavarian physicians chamber. The clinical part of the study was carried out by LAB GmbH (NeuUlm; Germany).

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For evaluation of the plasma concentrations of PGE_1, PGE_0 and 15-keto-PGE_0, blood samples were drawn 30, 15 and 1 min before and 5, 10, 30, 60, 90, 115, 125, 130, 150, 180 and 240 min after the start of infusion. A highly specific and sensitive GC/MS/MS-method was used for the measurement of plasma concentrations [1]. The validated analytical method with a calibration range of 1–100 pg ml^{-1} (PGE_1 and PGE_0) and 10–1000 pg ml^{-1} (15-keto-PGE_0) has an accuracy with a standard deviation <10%. The lower limit of quantification is 1 pg ml^{-1} (PGE_1 and PGE_0) and 5 pg ml^{-1} (15-keto-PGE_0).

An arithmetic mean of the three endogenous plasma concentrations before the start of the infusion was selected as the endogenous baseline.

C_{max} (individual maximum of plasma concentrations) was taken directly from the data, whilst the area under the concentration-time-curve (AUC(0,240 min)) was calculated by the linear trapezoidal rule. The dose dependency of plasma concentrations of PGE_1, PGE_0 and 15-keto-PGE_0 was calculated by subtraction of endogenous plasma levels from measured levels during and after the infusion.

The dose linearity of baseline and dose-corrected C_{max} and AUC values was investigated by ANOVA (SAS software version 6.10) with a level of significance of 5%.

Total clearance of PGE_1 was calculated by the ratio of dose and net AUC. As the fraction f of the dose metabolised to PGE_0 or 15-keto-PGE_0 is not known we only give dose normalized net AUC for the metabolites.

Results

Medical observations during the study

The subjective and objective drug effects were of a mild to moderate intensity. The symptom most often observed was a reddening of the upper arm vein, proximal to the infusion site. Further symptoms found in individual cases were dragging pain from the upper arm to the neck, feeling of pressure and warmth in the lower arm, general feeling of warmth connected with face reddening and headache. These side effects are well-known from the literature [10].

Changes in safety parameters (blood pressure, heart rate) after drug application remained within the normal physiological range (mean blood pressure and heart rate varied with ± 3 mm Hg or beats min^{-1}).

Plasma concentrations of PGE_1, PGE_0 and 15-keto-PGE_0

During the intravenous infusion of PGE_1, endogenous plasma concentrations increased from 1.7 ± 0.8 pg ml^{-1} (mean ± s.d.) within only a few minutes to the steady state plasma concentrations.

Figure 1 shows the mean plasma concentrations during and after infusion of the three doses of PGE_1.

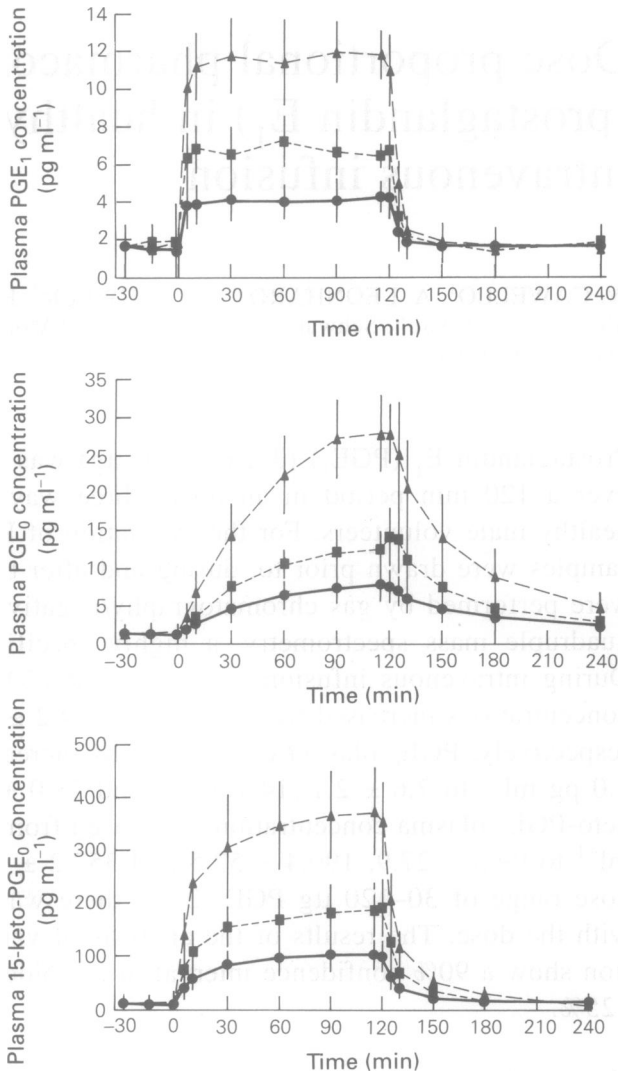

Figure 1 PGE_1, PGE_0 and 15-keto-PGE_0 plasma concentrations before, during and after intravenous infusion of different doses of PGE_1 (● 30 µg, ■ 60 µg, ▲ 120 µg) in healthy male volunteers (mean ± s.d., n = 12).

Values for C_{max}, AUC and clearance are given in Table 1.

The evaluation of the individual net PGE_1 plasma concentrations demonstrate a proportional increase of C_{max} and AUC with increasing doses of PGE_1. The results of the analysis of variance after baseline and dose-correction show a 90% confidence interval in the bioequivalence acceptance range of 80 to 125%. For example confidence intervals of PGE_1 AUC(0,240 min) after doses of 30, 60 and 120 µg were 89.9–120.9%, 80.6–111.6% and 83.0–114.0% respectively.

Plasma concentrations of PGE_0 increased from the endogenous level of 1.3 ± 1.0 pg ml^{-1} to steady state (Figure 1). Making an allowance for endogenous concentrations, there is a proportional increase of C_{max} and AUC with increasing doses of PGE_1.

15-keto-PGE_0 also has a dose related plasma concentration-time course (Figure 1). Plasma concentrations increased from endogenous levels of 10.2 ± 13.9 pg ml^{-1} up to steady stage plasma concentrations

Table 1 Pharmacokinetic parameters of PGE_1, PGE_0 and 15-keto-PGE_0 after intravenous infusion of PGE_1 in healthy subjects (mean ± s.d.)

Parameter	*Dose of PGE_1 (μg)* 30	60	120
PGE_1			
C_{max} (pg ml^{-1})	4.8 ± 1.0 (3.4–6.3)	7.7 ± 1.2 (6.7–10.8)	12.9 ± 1.7 (10.2–14.6)
AUC(0,240 min) (pg ml^{-1} min)	694 ± 201 (462–1169)	1016 ± 164 (840–1342)	1606 ± 220 (1239–1930)
CL (l min^{-1})	108.8 ± 48.8 (60.2–193.9)	105.3 ± 19.9 (79.6–144.3)	102.9 ± 19.9 (77.7–147.2)
PGE_0			
C_{max} (pg ml^{-1})	8.3 ± 2.2 (5.3–12.0)	15.1 ± 4.0 (8.7–22.8)	29.2 ± 4.7 (22.76–37.2)
AUC(0,240 min) (pg ml^{-1} min)	1172 ± 379 (789–2022)	1854 ± 458 (1186–3066)	3710 ± 748 (2900–4934)
Dose normalised AUC (pg ml^{-1} min μg^{-1})	28.7 ± 8.4 (19.0–47.5)	25.8 ± 4.9 (16.2–31.4)	28.1 ± 5.9 (21.5–39.1)
15-keto-PGE_0			
C_{max} (pg ml^{-1})	108.6 ± 28.8 (79.4–191.0)	203.6 ± 51.7 (134.5–301.5)	395.6 ± 81.8 (301.1–558.1)
AUC(0,240 min) (pg ml^{-1} min)	13387 ± 5046 (8429–27739)	23051 ± 6335 (16273–38887)	44544 ± 9107 (33060–66549)
Dose normalised AUC (pg ml^{-1} min μg^{-1})	365.0 ± 73.8 (255.4–528.6)	339.1 ± 63.3 (263.6–470.6)	346.4 ± 81.5 (233.1–512.6)

within 2 h of infusion. Endogenous plasma concentrations were measured again 2 h after ending the infusion.

Discussion

The observed results are consistent with the pharmacokinetics of PGE_1 described in the literature [1, 6, 11, 12]. The rapid increase of plasma concentrations during infusion and the rapid fall post infusion corresponds with the published short terminal half-lives [7, 11].

C_{max} and AUC(0,240 min) values of PGE_1, PGE_0 and 15-keto-PGE_0 were not different after dose normalization of net plasma concentrations. In addition total body clearance was similar for all doses.

Therefore, we have demonstrated that the pharmacokinetics of PGE_1, PGE_0 and 15-keto-PGE_0 during and after intravenous infusion of PGE_1 in healthy volunteers do not alter in the dose range 30–120 μg $2\ h^{-1}$.

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