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Pharmacokinetics of intravenous fluticasone propionate in healthy subjects

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1 Fluticasone propionate (FP) is a potent glucocorticoid used in the treatment of asthma. Prior to reporting the pharmacokinetics following the inhaled and oral routes, the pharmacokinetics need to be established following intravenous dosing. The present study determines the intravenous pharmacokinetics of FP, using non-compartmental analysis, in healthy male subjects over the 250 to 1000μg dose range.

2 The pharmacokinetics of FP can be regarded as being linear over this dosing range. FP was extensively distributed within the body (V_{ss} 318 l), rapidly cleared (CL 1.1 l min^{-1}) with a terminal elimination half-life of 7.8 h and a mean residence time of 4.9 h.

3 In order that future pharmacokinetic/pharmacodynamic and other modelling can be carried out, the plasma concentration-time profiles were parameterized using a model based on sums of exponentials, the appropriateness of this model was justified as the secondary kinetic parameters from the model were similar to those obtained using non-compartmental analysis.

Keywords glucocorticosteroid fluticasone propionate pharmacokinetics healthy subjects intravenous

Introduction

Fluticasone propionate (FP) is a highly potent lipophilic glucocorticoid which was designed to be metabolically labile and have a low oral bioavailability thus minimizing systemic effects e.g. reductions in plasma cortisol. Studies in rats and mice have shown FP to have a high topical to systemic activity ratio [1]. In clinical studies FP has been found to be topically effective in the treatment of asthma and allergic rhinitis [2], where the maximum single inhaled dose is 1000μg day^{-1}.

The pharmacokinetic parameters of FP need to be established following intravenous dosing, this is important for simulations and pharmacokinetic/pharmacodynamic modelling purposes. The present study will establish whether the distribution and elimination processes of FP in the systemic circulation are linear. Therefore, any non-linearity observed following either the oral or inhaled routes of administration must be attributed to some other process than distribution and elimination. The inhaled bioavailability following a metered dose inhaler is approximately 26% and the average oral bioavailability is less than 1% [3].

Preliminary pharmacokinetics of intravenous FP (2000μg dose) were investigated early in the drug's development [4]. However, in recent years the assay's lower limit of quantification has been improved from 0.13 ng ml^{-1} to 0.05 ng ml^{-1} along with its precision and accuracy. The present paper reports the intravenous pharmacokinetics of FP in healthy male subjects over the 250 to 1000μg dose range from five clinical studies.

Methods

Study design

Study 1 Twelve healthy male volunteers, mean age 28 years (range 21–38 years) and mean weight 75kg (range 55–100kg) received in a double-blind cross-over study, single doses of 250, 500 and 1000μg intravenous FP as 3 min infusions.

Studies 2–5 In total, 48 healthy male volunteers (12 subjects in each study), mean age 23 years (range 18–42

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years) and mean weight 77kg (range 58–99kg) received, single 250μg intravenous doses of FP as 3 min infusions.

For entry into each study the volunteers had to be within 15% of ideal body weight, non smokers and have an alcohol intake less than 4 units per day. Studies 1 to 3 inclusive were approved by the Glaxo Independent Ethics Committee and studies 4 and 5 were approved by the Pharma Bio-Research Independent Ethics Committee. Written informed consent from each volunteer was obtained prior to the studies commencing. The studies were conducted in accordance with the provisions of the Declaration of Helsinki and revisions. Tolerability was assessed by the incidence of adverse events reported.

FP was formulated in 50 ml of 20% human serum albumin containing 0.4 ml ethanol. Blood samples (6.5 ml) for plasma FP determination were taken predose (within 10 min of dosing), 3, 4, 5, 6, 8, 10, 15, 20, 30, 45 min and 1, 2, 3, 4, 6, 8, 12, 16, 20 and 24 h post-dose.

Drug assay

Plasma FP concentrations were measured by radioimmunoassay [5] at Simbec Research Limited, UK. The assay's lower limit of quantification was 0.05 ng ml^{-1} and the intra- and inter-batch coefficients of variation were <9 and $<17\%$ respectively.

Pharmacokinetic analysis

The data were analysed by a conventional non-compartmental approach [6] using SIPHARM, an in-house PC based pharmacokinetic package which incorporates SIPHAR (Release 3/88).

In study 1 the exponential equation ($C(t)=\Sigma\, C_i e^{-\lambda it}$) with a weighting scheme $\frac{1}{C^2}$ was fitted to the data using SIPHAR (Release 4). AUC(0,∞) was calculated using the coefficients and exponents obtained from the above fitting $\left(\Sigma\, \frac{C_i}{\lambda_i}\right)$. C_i and λ_i are the last quantifiable plasma concentration and rate constant respectively. Plasma clearance (CL) and apparent volume of distribution at steady-state (V_{ss}) were calculated by conventional equations.

Statistical analysis

For comparative purposes AUC(0,8h) rather than AUC(0,∞) was chosen as data beyond 8 h for the 250 μg dose were below the assay's lower limit of quantification. The values for C_{max}, AUC(0,8h) and AUC(0,∞) were logarithmically transformed and dose-normalised prior to analysis by analysis of variance which allows for effects due to subjects, periods and treatments. The estimates and 90% confidence intervals (CIs) of the dose-normalised C_{max} and AUC(0,8h) ratios following the 250 and 500 μg doses and the 1000 and 500 μg were obtained. The dose normalised parameters were considered to be similar if the 90% CIs lay between 80–125% i.e. using the criteria for bioequivalence testing [7].

Results

All the doses of FP were well tolerated by the subjects and no serious adverse events were reported in the study.

Figure 1 shows the plasma concentration-time profiles following 250, 500 and 1000 μg intravenous doses given as 3 min infusions. Table 1 summarises the non-compartmental analysis and exponential fitting results. The model parameters (geometric means and 95% CI) for the 1000 μg dose are C_1 100.59 (72.60–139.35), λ_1 21.64 (17.85–26.24), C_2 4.17 (3.47–5.00), λ_2 0.750 (0.486–1.158), C_3 0.439 (0.258–0.748), λ_3 0.0875 (0.0631–0.1213).

From Figure 1 it can be observed that the plasma concentration-time profiles following the highest dose was best described by three exponentials (i.e. three phases on a semi-logarithmic scale). In comparison, the 250μg dose was best described by two exponentials because the plasma concentrations after 8 h post-dose were generally below the assay's lower limit of quantification. The dose-normalised median plasma profiles up to 8 h were superimposable for the three doses, suggesting that the pharmacokinetic parameters can be regarded as being dose proportional. This was confirmed from the statistical analysis, the 90% CIs for dose-normalised AUC(0,8h) were within the 80–125% limits: 250/500 μg comparison, 90% CI 86–98%, 1000/500 μg comparison 90% CI 92–104% and 250/1000μg comparison 90% CI 88–100%. For C_{max} the 90% CI of the ratios for 1000/500 μg

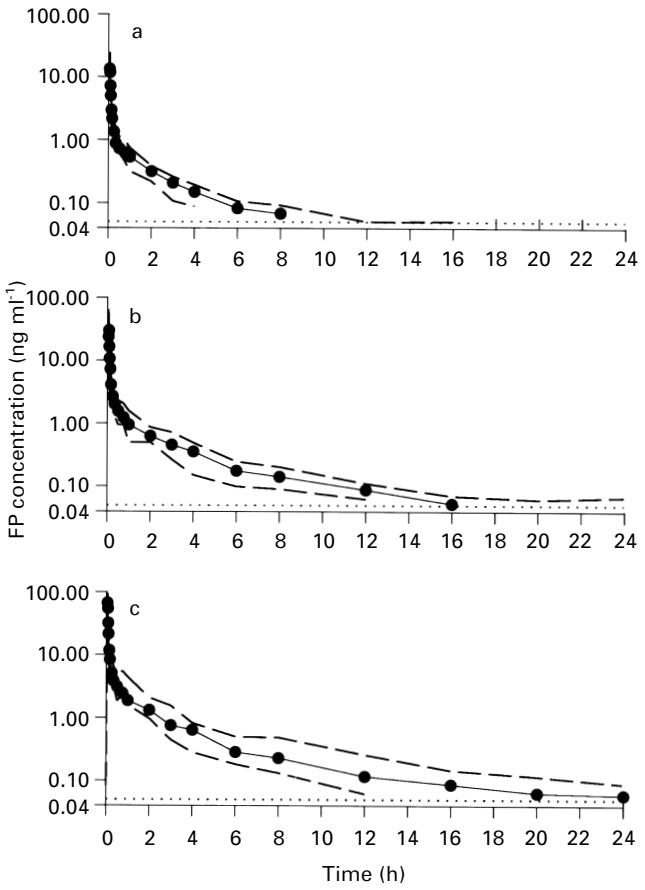

Figure 1 Median and range of plasma fluticasone propionate concentrations following a) 250 μg, b) 500 μg and c) 1000 μg intravenous doses (study 1, $n = 12$). … LLQ (0.05 ng ml^{-1}), —●— median.

Table 1 Pharmacokinetic parameters of intravenous fluticasone propionate (geometric mean and 95% CI) following 1000, 500 and 250 μg intravenous doses using both non-compartmental and exponential analysis (Study 1, $n=12$)

	Non compartmental analysis			*Exponential fitting*		
	Dose			*Dose*		
Parameter	*1000 μg*	*500 μg*	*250 μg*	*1000 μg*	*500 μg*	*250 μg*
C_{max}*	63.7	32.8	12.8	63.7	32.8	12.8
(ng ml^{-1})	(50.2–80.8)	(25.0–42.9)	(8.8–18.6)	(50.2–80.8)	(25.0–42.9)	(8.8–18.6)
AUC (0,8h)	12.2	6.2	2.9			
(ng ml^{-1} h)	(10.8–13.7)	(5.5–7.1)	(2.6,3.2)			
AUC(0, ∞)	145	8.0	3.3	15.9	8.8	3.5
(ng ml^{-1} h)	(12.9–16.4)	(6.9–9.3)	(2.9–3.7)	(14.2–17.8)	(7.5–10.2)	(3.0–4.0)
CL (l min^{-1})	1.15	1.04	1.26	1.05	0.95	1.20
	(1.02–1.29)	(0.90–1.21)	(1.11–1.44)	(0.93–1.17)	(0.82–1.11)	(1.05–1.37)
$t_{1/2,z}$†	7.15	8.45	3.43‡	7.92	8.47	1.84‡
(h)	(5.5–9.37)	(5.46–13.08)	(2.13–5.50)	(2.71–10.98)	(5.04–14.24)	(1.49–2.27)
MRT_{iv}	4.2	5.6	2.8‡	4.27	5.09	2.12‡
(h)	(3.5–5.0)	(3.6–8.7)	(1.8–4.4)	(3.58–5.08)	(3.28–7.89)	(1.51–2.96)
V_{ss}	287	349	213‡	268	290	152‡
(l)	(233–354)	(238–510)	(144–315)	(219–329)	(191–441)	(111–209)

* Values taken directly from plasma concentration-time curve

† Terminal exponential.

‡ Note for the μg dose there are only two exponentials compared with three exponentials for the 1000 and 500μg doses, explaining the differences in the parameters

comparison was 81–117%, for the 250/500 μg comparison was 65–94% and for 250/1000 μg comparison was 67–96%. The latter comparisons were the only ones outwith the 80–125% limits, however AUC(0,8h) is regarded as a much more robust parameter compared with C_{max}. Therefore the pharamacokinetics of intravenous FP can be regarded as being proportional to dose.

Because of the incomplete description of the plasma FP concentration-time profile following the 250 μg dose, the definitive intravenous FP pharmacokinetic parameters were determined by averaging the geometric means following the 500 and 1000 μg doses from non-compartmental analysis. FP was extensively distributed within the body (V_{ss} 318 l) and rapidly cleared (CL 1.1 l min^{-1}). The mean residence time was 4.9 h and the terminal elimination half-life was 7.8 h.

As all the studies using the 250 μg intravenous dose were conducted using an homogenous population of subjects, using identical study procedures in only two different centres, the 95% CI around the pharmacokinetic parameter population mean represents the population variability between subjects. Thus, the individual clearance values from studies 1 to 5 (ie a total of 60 subjects), were pooled together and 95% CI were calculated. The resulting plasma clearance (geometric mean and 95% CI) was estimated to be 1.0 l min^{-1} (0.9–1.1 l min^{-1}).

Discussion

The pharmacokinetics of intravenous FP have been investigated over a range of doses (250–1000 μg) using both non-compartmental and exponential fitting methods. There was good agreement between the two methods in terms of the secondary pharmacokinetic parameters, therefore supporting the appropriateness of the PK model parameters for future modelling work. The kinetic parameters C_{max} and AUC from the dose-normalised plots and the statistical analysis, were proportional to dose over the 250 to 1000 μg range investigated, suggesting that the metabolism of FP was not saturated.

With the increase in the sensitivity, precision and accuracy of the FP assay, the intravenous FP data could be best described by the sum of three exponentials. Peak plasma concentrations of FP were reduced by approximately 98% within 3–4 h and the terminal elimination half-life was 7.8 h. However, because of the polyexponential kinetics, only very low plasma concentrations (<0.2 ng ml^{-1}) were associated with the terminal elimination half-life. This third phase may represent the slow dissociation of FP from the tissue components which may be a consequence of the high lipophilicity of the drug. A pharmacokinetic/pharmacodynamic model is being developed to assess whether these low plasma concentrations of FP contribute to any systemic effects.

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