Plasma concentrations of betamethasone after topical application of betamethasone 17-valerate: comparison with oral administration

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Plasma concentrations of betamethasone were measured by r.i.a. after oral administration of 0.6 mg betamethasone and topical application of betamethasone 17-valerate in the same five healthy subjects. Betamethasone 17-valerate was prepared as a suspension in medical grade pressure sensitive adhesive and applied to a 100 cm² area on the back for 28 h. Mean maximum plasma concentrations were 5.0 and 0.24 ng ml⁻¹ and mean AUC values were 75.4 and 7.74 ng ml⁻¹ h after oral and topical administrations, respectively. The mean plasma elimination half-life of betamethasone after the removal of topical betamethasone 17-valerate was 16.6 h which was twice that after oral administration, 8.1 h. Betamethasone 17-valerate may require application to the skin more than twice daily.

Keywords corticosteroid betamethasone 17-valerate betamethasone percutaneous absorption pharmacokinetics

Introduction

The pharmacokinetics of topical corticosteroids are not well understood despite their extensive use. This is partly because of difficulty in measurement of corticosteroid in the plasma or urine after topical application [1]. In this study, plasma concentrations of betamethasone were measured by a sensitive r.i.a. method after the oral administration of betamethasone and topical application of betamethasone 17-valerate in the same individuals.

Methods

Subjects

Five subjects (four males and one female), aged 26 to 30 years weighing from 60 to 88.5 kg (average, 75.8 kg) entered the study after giving their informed consent. The study was approved by the Committee on Human Research of the University of California at San Francisco. Each subject was judged to be in good health on the basis

of a medical history, physical examination and standard clinical laboratory tests.

Administration of oral betamethasone and topical betamethasone 17-valerate

Each subject received a single oral administration of 0.6 mg (one tablet) of betamethasone (Celestone[®], Schering Corporation, Kenilworth, NJ, USA) and also a single topical application of 0.8% (w/v) betamethasone 17-valerate in medical grade pressure sensitive adhesive, BIO-PSA[®] (Dow Corning, Midland, MI, USA). The two dosages were given in a randomized fashion at least 2 weeks apart. After the oral administration of betamethasone, peripheral venous blood samples were collected at 0 (predose), 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10 and 24 h. Betamethasone 17-valerate was suspended in BIO-PSA[®] (solubility $\approx$ 0.1% (w/v)) and the vehicle thickness was 50 μ m [2]. Therefore, this BIO-PSA[®] contained 4 mg betamethasone 17-valerate over a 100 cm² area (40 μ g cm⁻²). Betamethasone 17-valerate was applied to the 100 cm² area of the subject's back and removed at 28 h.

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Venous blood samples were collected at 0, 4, 8, 12, 24, 28, 32, 48, 52, 56 and 72 h.

Radioimmunoassay

Plasma betamethasone was measured by a modified radioimmunoassay originally developed for plasma dexamethasone [3]. The standard was betamethasone (Sigma, St Louis, MO) and was used in a range of 1 pg/tube–256 pg/tube. Twenty-four of 25 steroids and their metabolites showed negligible cross-reactivity ($< 0.05\%$). Dexamethasone (the 16- α methyl isomer of betamethasone) showed a cross-reactivity of 206%. Consistently high correlation coefficients ($r > 0.998$) were obtained in five consecutive standard curves. The limit of determination was less than 1 pg betamethasone per r.i.a. tube. Plasma samples were assayed in duplicate using 25 or 100 μ l/tube for oral or topical experiments, respectively. Linearity ($r = 0.9986$ – 1.0000) was demonstrated between plasma dilutions (1:1 to 1:16) and betamethasone concentrations. The precision of measurements for samples from oral (measured at 0.7 to 6.4 ng ml $^{-1}$) and topical (at 0.014 to 0.43 ng ml $^{-1}$) administration was $< 5\%$ (within-assay) and $< 10\%$ (between-assay), respectively.

Data analysis

$C_{\max}$ and $t_{\max}$ values were noted directly from the data. The terminal elimination half-life ($t_{1/2,z}$) was estimated by log linear regression. AUC was obtained by the linear trapezoidal method with extrapolation to infinity. A first-order absorption rate constant (k_a) was estimated by fitting the oral administration data with a one compartment model using a non-linear least squares method [4] with no weighting.

Results

Mean plasma drug concentrations after the oral administration of betamethasone (0.6 mg) are shown in Figure 1a. Those after the topical application of betamethasone 17-valerate are shown in Figure 1b. The pharmacokinetic parameters are listed in Table 1. Mean $C_{\max}$ and AUC values after the oral administration were 20 and 10 times greater than those after the topical application, respectively. The mean terminal half-life after the removal of betamethasone 17-valerate was twice that after oral administration of betamethasone.

Discussion

The pharmacokinetic parameters after oral administration (Table 1) were compatible with those reported previously [5, 6]. If the oral bioavailability (F) of betamethasone is assumed to be complete [5], and if it is assumed that plasma betamethasone is derived from betamethasone 17-valerate, the AUC value observed after topical application suggests that 62 μ g betamethasone equivalent was absorbed over 28 h from the 100

Figure 1 Mean ($\pm$ s.e. mean) plasma betamethasone concentrations in the same five subjects after the oral administration of betamethasone (0.6 mg) (a) and 28 h topical application of 0.8% (w/v) betamethasone 17-valerate suspension in silicone adhesive to a 100 cm 2 area of the back (b).

Table 1 Parameters describing the pharmacokinetics of betamethasone after oral administration of 0.6 mg betamethasone and topical application of 0.8% (v/w) betamethasone 17-valerate to a 100 cm 2 area in 5 healthy subjects

	Mean*	Range
<i>Oral administration</i>		
$C_{\max}$ (ng ml $^{-1}$)	5.0	4.4–5.1
$t_{\max}$ (h)	2§	1–3
AUC (ng ml $^{-1}$ h)	75.4	69.7–83.1
$t_{1/2,z}$ (h)	8.1 [†]	6.7–9.3
k_a (h $^{-1}$)	1.72	0.73–2.94
<i>Topical application</i>		
$C_{\max}$ (ng ml $^{-1}$)	0.24	0.09–0.43
$t_{\max}$ (h)	28§	24–32
AUC (ng ml $^{-1}$ h)	7.74	2.71–16.80
$t_{1/2,z}$ (h)	16.6 [†]	11.0–21.1

*Unless otherwise specified.

§Median value.

[†]95% confidence interval on difference between two routes of administration = 4.8–12.3 h.

cm 2 skin area. The mean plasma concentration between 24 to 32 h after topical application was approximately 0.18 ng ml $^{-1}$ which corresponded to an absorption rate of 1.4 μ g h $^{-1}$ or 14 ng h $^{-1}$ cm $^{-2}$ when measured as betamethasone. The difference in plasma half-life of

betamethasone between the two routes of administration suggests that further drug is being absorbed from the skin site into the circulation after removal of the topical application. The half-life after removal of the topical 17-

valerate was less than 24 h in our healthy subjects indicating that betamethasone 17-valerate may require application to the skin more than twice daily unless the skin surface is protected.

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