Pharmacokinetics of Dexamethasone in a Rat Model of Rheumatoid Arthritis

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Abstract

Dexamethasone (DEX) is often given for the treatment of rheumatoid arthritis and clinical dosing regimens of DEX have often been based empirically. This study tests whether the inflammation processes in a rat model of rheumatoid arthritis alters the clearance and volume of distribution of DEX when compared with healthy controls. Groups of healthy and arthritic male Lewis rats received either a low (0.225 mg/kg) or high (2.25 mg/kg) intramuscular dose of DEX. Arthritis was induced by intradermal injection of type II porcine collagen in incomplete Freund's adjuvant emulsion at the base of the tail. DEX was dosed in the arthritic animals 22 days post arthritis induction. Plasma DEX concentrations were determined by HPLC. Plasma concentration versus time data were analysed by non-compartmental analysis and pharmacokinetic model fitting using the population pharmacokinetic software NONMEM V. A linear bi-exponential pharmacokinetic model with extravascular input described the data for both healthy and arthritic animals. Clearance was the only parameter determined statistically different between both groups (healthy=1.05 l/h/kg, arthritic=1.19 l/h/kg). The steady-state volume of distribution for both groups was 4.85 l/kg. The slight difference in clearance was visibly undetectable and unlikely to produce meaningful changes in DEX disposition in arthritic rats.

Keywords

dexamethasone; pharmacokinetics; arthritis; collagen

Introduction

Glucocorticoids were discovered for the treatment of rheumatoid arthritis (RA) in 1949 and today their synthetic analogs, corticosteroids, remain a mainstay in treatment of the disease [1–3]. Dosing of these compounds has often been based empirically. Dexamethasone (DEX) is very potent in this class of drugs having a fluorinated structure and increased affinity for the glucocorticoid receptor [2–5]. While the kinetics of DEX in healthy individuals and patients with arthritis are well characterized, the pharmacokinetics (PK) of this drug in various animal models of rheumatoid arthritis has not been examined.

Animal models of RA are valuable as a means to quantify disease progression and drug effect as measured by specific molecular biomarkers and disease endpoints. Although not a complete model of the genetically complex disease in humans, these models offer insight into a specific pathology of RA and chronic inflammation [6]. Collagen-induced arthritis in

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the Lewis rat is a recent and clinically relevant model of RA [6–8]. Rats can be utilized for destructive tissue sampling and a rich set of time dependent drug-effect data may be generated. Before DEX concentrations can be related to the effect in these arthritis models, its PK need to be appreciated. Additionally, such PK data may lend insight into the mechanisms of drug distribution and elimination potentially relevant to the clinical scenario.

Inflammation affects many organs throughout the body. Chronic inflammation can possibly alter the clearance, distribution, and unbound and total plasma concentrations of DEX. Garg *et al.* showed a 2.4-fold decrease in clearance and a reduction of 10–30% in the plasma protein binding of prednisolone elevating both total and free concentrations of the steroid in animals with carrageen-induced chronic inflammation. Acute and chronic inflammatory conditions in rats have caused changes in liver expression of enzymes such as cytochrome P450 isozymes and p-glycoprotein relevant to the *in vivo* metabolism and distribution of DEX [3,9–12]. Piquette-Miller showed that hepatic PGP expression was reduced 50–70% following administration of LPS in the rat. Assenat *et al.* and Pascussi *et al.* showed that TNF-α, IL-1β and IL-6 inhibit constitutive androstane receptor (CAR) and pregnane x-receptor expression (PXR), reducing CYP450 expression in primary human hepatocytes and that NF-κB interferes with the glucocorticoid response element located in the promoter regions of CAR and PXR genes. Vuppugalla noted an acute inhibitory effect of nitric oxide on cytochrome P450 activity. Furthermore, Ling *et al.* demonstrated reduced clearance of verapamil by cytochrome P450 isozymes in early phase adjuvant induced arthritis in the rat. Wang *et al.* showed a redistribution of macromolecules from blood to inflamed tissue during adjuvant arthritis in the rat, potentially explaining the decrease in plasma protein binding observed by Garg *et al.* for prednisolone. Thus inflammation in an animal model of arthritis could reduce the clearance, alter the distribution and decrease the plasma protein binding of DEX [13–19].

This study compares the PK of DEX in a rat model of rheumatoid arthritis with the kinetics of DEX in healthy rats. The time course of plasma concentrations is presented for both healthy and arthritic rats receiving 2.25 and 0.225 mg/kg intramuscular (IM) DEX. A PK model was developed to test for differences in parameters between treatment groups. Lewis rats were examined at the occurrence of peak peripheral joint edema.

Methods

Materials

Dexamethasone sodium phosphate was obtained from Henry Schein, Inc. (Melville, NY). Type II porcine collagen dissolved to 2 mg/ml in 0.5 M acetic acid was purchased from Chondrex, Inc. (Redmond, WA). Incomplete Freund's adjuvant was purchased from Sigma Aldrich (St Louis, MO).

Animals

Forty-eight male Lewis rats, age 6–9 weeks, were purchased from Harlan Sprague Dawley, Inc. weight matched to approximately 150 g. Animals were housed individually in the University Laboratory Animal Facility and acclimatized for 1 week under constant temperature (22°C), humidity (72%) and circadian light cycle (12 h light/12 h dark). Rats had free access to rat chow and water. All protocols followed Principles of Laboratory Animal Care (National Institute of Health publication 85-23, revised 1985) and were approved by the University at Buffalo Institutional Animal Care and Use Committee.

Induction of collagen induced arthritis

The induction of collagen induced arthritis (CIA) in Dark Agouti and Lewis rats followed protocols supplied by Chondrex, Inc. Porcine collagen type II (2 mg/ml) in 0.05 M acetic acid was emulsified with incomplete Freund's adjuvant using an electric homogenizer (Virtis) equipped with a blade of 10 mm diameter. Equal amounts of collagen (2 mg/ml) and Incomplete Freund's Adjuvant (IFA) were mixed in an ice water bath, adding the collagen drop-wise to the IFA at low speed. The Virtis speed was increased to 30 000 rpm for 2.5 min, then 0 rpm for 2.5 min, and a final mix at 30 000 rpm for 2.5 min. The emulsion was ready when it appeared to be a stiff white substance that congealed instead of dissipating when dropped in water. Thirty-two rats were anesthetized with ketamine/xylazine (75/10 mg/kg) and received 0.2 ml of collagen emulsion by intra-dermal injection at the base of the tail. Booster injections were administered on day 7 of the study with 0.1 ml emulsion at the same injection site. Disease status was measured by monitoring hind paw swelling and body weight on study days 9, 12, 15, 17, 19, 20, 21, 22 and 23.

Dexamethasone pharmacokinetic study

The PK of DEX was compared in arthritic rats and healthy controls. Healthy and arthritic male Lewis rats were dosed intramuscularly with either 0.27 or 2.7 mg/kg dexamethasone phosphate in saline (equivalent to 0.225 and 2.25 mg/kg dexamethasone). Animals with CIA were dosed 22 days post disease induction immediately after the peak edema in the hind paw was observed. On study day 21 arthritic rats underwent surgery to externally cannulate the jugular vein. Healthy animals underwent cannulation 1 week after arrival and 1 day prior to dosing. During surgery the rats were anesthetized with ketamine/xylazine (75/10 mg/kg). External cannulas were kept clear and functional with EDTA in saline (1.5 mg/ml).

To supply the desired number of sample times without taking too much blood from each rat, two sets of sampling schedules were used (A and B). Thirty-two rats were used in the study. Each disease group (CIA, healthy) had two dose levels (0.27, 2.7 mg/kg). Each dose level had two sampling schedules (A, B) with four rats in each group. Collagen was administered to 32 rats to ensure CIA developed in 16 animals, expecting an incidence of about 60%. Four rats that had developed arthritis by study day 17 were assigned to each dosing schedule for each dose level for a total of eight rats to be serial sampled for each dose level. Animals were considered to have developed arthritis if hind paw edema was clearly visible and swollen more than 150%, as measured by digital calipers, in both paws. Animals in dosing schedule A were sampled at 10 and 30 min, 1, 2, 4 and 8 h post dose with an additional 24 h time point in the high dose group. Animals in dosing schedule B were sampled at 20 and 45 min, 1.5, 3, 6 and 12 h post dose with an additional 24 h time point in the high dose group. Rats were killed at their last sample time by aortal exsanguinations under ketamine/xylazine anesthesia. Blood was collected in syringes containing sufficient EDTA to yield 1.5 mg/ml (4 mM) final concentration [20]. Samples were centrifuged at $1800 \times g$ for 10 min at 4°C. Plasma was collected and stored at –20°C.

Corticosteroid extraction and HPLC analysis

Rat plasma was thawed and 0.1–1.0 ml aliquots were extracted with methylene chloride in 7 ml glass Pyrex tubes (Corning Glass Works, Corning, NY). Tubes were shaken for 45 min before washing the methylene chloride phase with 0.5 ml of 0.1 N sodium hydroxide. The NaOH phase was removed following centrifugation and the methylene chloride phase was washed twice with 0.5 ml water, discarding the water after each wash. Methylene chloride was evaporated off with purified air, leaving a residue that was reconstituted in 110 µl of mobile phase. Chromatography conditions involved a mobile phase of 600 ml methylene chloride, 350 ml heptane, 10 ml glacial acetic acid and 54 ml ethanol, a Zorbax normal phase column, Waters model 1515 isocratic pump and Waters model 2487 dual λ

absorbance detector [21]. The lower limit of quantification was 5 ng/ml with an intra-day coefficient of variation of less than 10%.

Pharmacokinetic data analysis

Plasma concentrations of DEX were modeled as a function of time with a linear two-compartment mammillary PK model with first-order absorption input. Initial estimates were obtained by non-compartmental analysis using WinNonlin 5.0 (Pharsight Corp., Mountain View, CA). The Bailer–Satterthwaite method was used for determination of area under the curve (AUC_{0-24}) [22,23]. Both serial and sparse samples were available for analysis and this method permits a T-test comparison for sparse data using observed sample times versus nominal sample times, potentially reducing random error depending on the difference of the observed and nominal sampling times. The method employs a two-sided t-test to compare values of AUC_{0-24} between treatment groups for the same dose (Eq. (1))

$$t_{obs} = \frac{AUC_i - AUC_j}{\sqrt{s^2(AUC_i) + s^2(AUC_j)}} \quad (1)$$

where AUC_i is for healthy animals, AUC_j is for arthritic animals, and $s^2(AUC)$ is the variance of AUC_{0-24} for the respective groups. Intramuscular bioavailability (F) was determined previously and a value of 0.86 was used in the final model [24].

Model selection was made based on visual inspection of the data, goodness of fit plots and the Akaike Information Criterion (AIC). Figure 1 is a schematic of the final PK model used to fit the concentration—time data. Equations and initial conditions describing the amounts of DEX in each compartment are

$$\frac{dA_{Abs}}{dt} = -k_a \cdot A_{Abs}, \quad A_{Abs}(0) = \text{Dose} \cdot F \quad (2)$$

$$\frac{dA_{plasma}}{dt} = k_a \cdot A_{Abs} + \frac{CL_D}{V_T} \cdot A_T - \left(\frac{CL}{V_P} + \frac{CL_D}{V_P}\right) \cdot A_{plasma},$$

$$A_{plasma}(0) = 0 \quad (3)$$

$$\frac{dA_T}{dt} = \frac{CL_D}{V_P} \cdot A_{plasma} - \frac{CL_D}{V_T} \cdot A_T, \quad A_T(0) = 0 \quad (4)$$

where A_{abs} indicates the amount at the absorption site, A_{plasma} is the amount of DEX in plasma, A_T is the amount in peripheral tissues, k_a is the first-order absorption rate constant for i.m. administration, CL is the clearance from the plasma compartment, CL_D is the inter-compartmental clearance, V_P is the volume of distribution in plasma, V_T is the peripheral volume of distribution, and F is the i.m. bioavailability (0.86).

Concentrations of DEX in plasma were generated from

$$C_{plasma} = \frac{A_{Plasma}}{V_P} \quad (5)$$

The model was implemented in NONMEM VI using the ADVAN4 subroutine and TRANS3 parameterization. The model was fitted to data from each group independently and then simultaneously using the FOCE with interaction module in NONMEM VI. For the

simultaneous fitting conditional coefficients (FD_i) were added that corrected CL, CL_D, V, V_{SS} and k_a to the disease state values for animals with arthritis. Equation (6) describes the value that NONMEM implemented for pharmacokinetic parameters (CL, CL_D, V, V_{SS}, k_a) specified by P_i, in terms of the healthy population expected values (θ_i), correction coefficient for disease state (FD_i), and inter-animal variation (η_i) on plasma clearance (CL).

$$P_{i,\mathrm{dis}} = \theta_{i,\mathrm{healthy}} \cdot FD_i \cdot e^{\eta_i} \quad (6)$$

A χ^2 model discrimination test was done using differences in the minimum value of the objective function before and after removal of a model parameter to determine whether each disease coefficient had a significant impact on the model fitting. Significant differences between healthy and diseased animals were tested in terms of clearance and volume of distribution. If model parameters did not yield a difference in MVOF of greater than 3.86, they were removed and the disease was determined not to have a significant effect on that parameter [25].

Results and Discussion

Plasma PK of total DEX after i.m. administration was compared in normal and healthy arthritic rats. The concentration—time profiles for both healthy and arthritic rats receiving either 0.225 or 2.25 mg/kg i.m. DEX are shown in Figure 2. Dexamethasone absorption from the intramuscular site was rapid as the time of maximum concentration (t_{max}) was 0.5 h for all doses. Following peak concentrations, concentration data appeared to decline mono-exponentially in parallel between the dose groups. There appears to be little, if any, difference between the plasma concentrations of DEX in the healthy and the arthritic animals. The 12 and 24 h high dose concentrations from arthritic rats appear lower than the data from the healthy rats. This is in agreement with the results of the non-compartmental analysis for the high dose groups in Table 1 where the apparent clearance is larger for the arthritic animals with high dose. However, the apparent clearance appeared to be the same for the lower dose levels.

Non-compartmental analysis did not indicate any differences in the AUC_{0-24} between treatment groups for the same dose level. The Bailer–Satterthwaite AUC_{0-24} values and standard deviations are presented in Table 1. The t_{obs} value from Equation (1) was 0.518 for the low dose and 0.220 for the high dose values. The critical t-values were determined based on the Satterthwaite degrees of freedom for each dosing group to be 2.57 and 2.78 for the low and high doses [23,26]. In either dose group the t_{obs} was less than the critical t-value. Therefore, no statistical differences were concluded in AUC_{0-24} values between treatments for both doses ($\alpha = 0.05$). Dose normalization of the $AUC_{0-\infty}$ yielded similar values.

Initial inspection of t_{max} for each dose, linearity of the AUC values between doses, and the mono-exponential decline of the data suggested that the one-compartment mammillary model with first-order absorption was appropriate. However, a two-compartment linear model fitting yielded a lower value of AIC. The two-compartment model also better fitted the initial short distribution phase that is apparent in the arthritic low dose data (Figure 3, Panel B). Unlike corticosterone and prednisolone, DEX does not bind nonlinearly to transcortin [3,27]. Rather DEX is primarily bound linearly to albumin at about 70% in rats. This observation supports linear DEX kinetics. On the other hand, in humans plasma DEX concentrations exhibit a bi-exponential decline owing to a slower conversion of the phosphate ester prodrug to DEX [24]. In rats this process occurs so rapidly that it is not readily observed in the concentration—time profiles given the slightly delayed i.m. absorption.

Figure 3 shows the final two-compartment model fitting in both healthy (Panel A) and arthritic (Panel B) rats. Final PK parameter estimates are presented in Table 2. Clearance was the only model parameter that tested different between arthritic and healthy groups using the χ^2 model discrimination test by change in the MVOF with and without conditional disease factors present in the fitted model. The change in MVOF for clearance was 35.1 lower with the presence of a disease correction factor (FD_{CL}=1.13). Despite a significant difference noted by the NONMEM model fittings, the actual change in value of clearance is minor (1.13-fold increase).

These results were unexpected as earlier studies suggested a potential decrease in clearance and an increase in the plasma protein binding of DEX. A decrease in clearance would suggest that concentrations of DEX would remain elevated at later times. Instead it was observed that concentrations were lower at the later times and the clearance of DEX was in fact slightly higher than the healthy animals. If acute phase response proteins such as α1-acid glycoprotein, α2-macroglobulin, C-reactive protein, serum amyloid-A and others were elevated, it is possible that plasma DEX binding may no longer appear linear. In this case, one might expect a distinct early distribution phase to be noted for the lower doses. This may explain why, for the arthritic animals, a slight early distribution phase was noted. Additional doses would be required to confirm this and resolve parameters in a model sufficient to characterize this behavior. Due to only having data from two doses, variation in the data and the slightness of this distribution phase in the low arthritic dose, the two-compartment linear model exhibited the lowest *AIC* of all tested models. The availability of plasma in these animals was too limited to yield a thorough evaluation of DEX protein binding in plasma.

Earlier studies indicated that clearance may be decreased and the protein binding of DEX may be altered [14,15]. Results of these studies, however, were presented for no longer than the first 7 days of disease induction. Our animals were dosed on day 22 post induction immediately after the peak paw swelling. Since the mature state of collagen-induced model of arthritis is viewed as localized to the joints [6], it is possible that any acute phase response relevant to DEX PK occurred much earlier in the time course of progression and had diminished by 22 days post induction. Only a single point in the disease time course was evaluated. The kinetics of DEX at other time points of the disease progression should be established prior to evaluation of pharmacodynamic effects of the drug at those times.

Inter-animal variation was tested on clearance and volume parameters. In the final model, variation in the clearance of DEX best explained the inter-animal differences. A simple constant coefficient of variation model accounted for the random effects observed in the data.

Acknowledgments

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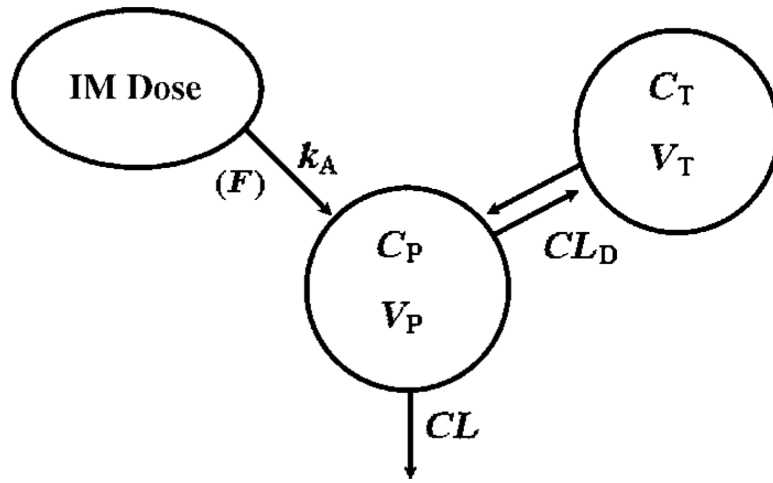
Figure 1.
Pharmacokinetic model for dexamethasone. Symbols are defined in the text and Table 2
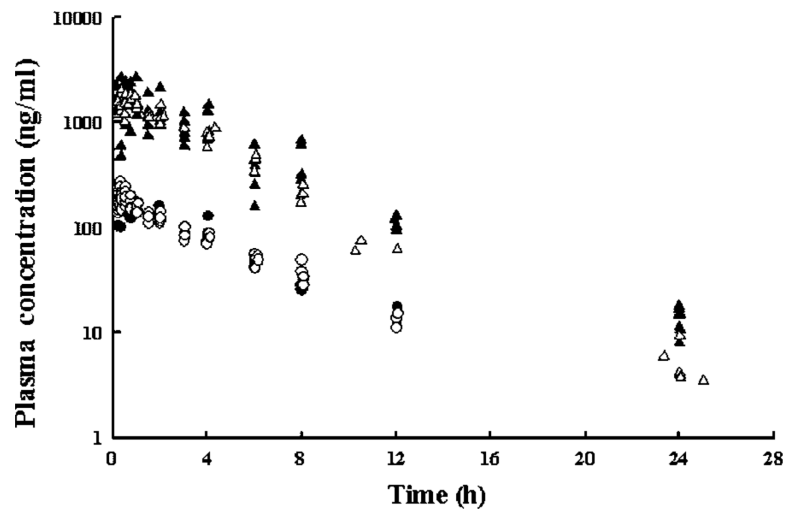
Figure 2.
Plasma concentration-time profiles of high (triangles) and low-dose (circles) dexamethasone in healthy (solid symbols) and arthritic (open symbols) rats
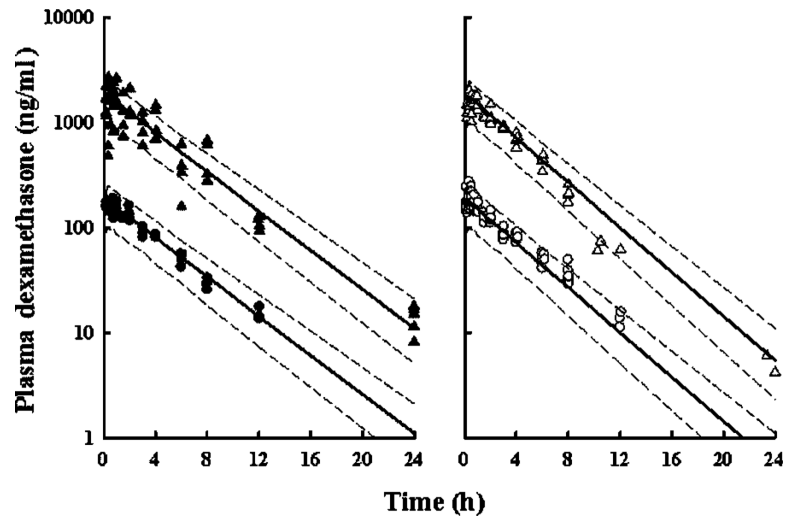
Figure 3.
Model fitting of low and high-dose plasma dexamethasone in healthy (Panel A) and arthritic rats (Panel B). Solid lines indicate the median population prediction of 1000 simulated individuals with the final population mean parameters for each dosing and treatment group. Dashed lines represent the 5 (lower) and 95 (upper) percentiles for each predicted plasma concentration time course

Table 1

Pharmacokinetic noncompartmental measures for i.m. dexamethasone

Parameter	Definition	Healthy		Arthritic	
		Dose, mg/kg: 2.25	0.225	2.25	0.225
λ_Z (h^{-1})	Terminal slope	0.157	0.164	0.165	0.187
C_{max} (µg/l)	Maximum concentration	1540	133	1460	168
$AUC_{0-Tlast}$ (µg h/l)	Area under curve	7700[a] (752)[b]	668[a] (21.8)[b]	6030[a] (112)[b]	683[a] (16.7)[b]
$AUC_{0-\infty}$ (µg h/l)	Area under curve	7760	733	6050	734
$AUC_{0-\infty}$/Dose	Dose-normalized AUC	3450	3260	2690	3040
CL/F (l/h/kg)	Apparent clearance	1.09	1.16	1.41	1.16
V_P/F (l/kg)	Apparent central volume	5.82	5.91	7.12	5.18

[a] Bailer–Satterthwaite area under curve.

[b] Standard error.

Table 2

Model pharmacokinetic parameter estimates for i.m. dexamethasone

Parameter	Definition	Estimate	SE %
CL_{Healthy} (l/h/kg)	Clearance in healthy Lewis rats	1.05	4.08
$CL_{\text{Arthritic}}$ (l/h/kg)	Clearance in arthritic Lewis rats	1.19	3.00
CL_{D} (l/h/kg)	Distributional clearance	7.20	42.5
V_{P} (l/kg)	Central volume of distribution	3.41	2.83
V_{SS} (l/kg)	Steady-state volume of distribution	4.85	3.17
k_{a} (1/h)	Intramuscular absorption rate constant	5.78	10.0
η_{CL}	Interanimal variation of clearance	0.0565	45.0
CCV	Slope of random error	0.215	18.3