Comparison of body surface area-based and weight-based dosing format for oral prednisolone administration in small and large-breed dogs

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Abstract

This study compared the pharmacokinetics of Prednisolone (PDS) in small- and large breed dogs with a dosing format based on body surface area (BSA) or body weight (BW). The maximum concentration and area under the curve in large-breed dogs orally administered 2 mg/kg PDS were significantly greater than those in small-breed dogs given 2 mg/kg and in large-breed dogs given 40 mg/m². The higher blood concentrations that result from BW-based dosing of oral PDS in large-breed dogs can be more than required for effect. Meanwhile, BSA dosing at 40 mg/m may be suboptimal. These findings confirm important differences between standard PDS dosing schemes in dogs while highlighting the need to further optimize PDS dosing in large-breed dogs.

Key words: body surface area, body weight-based, large-breed dog, pharmacokinetics, prednisolone

Introduction

Prednisolone (PDS) is the most commonly used oral glucocorticoid drug for dogs and cats. Traditionally, it is given by body weight (BW)-based dosing. This dosing format can lead to overdosing in large breed dogs because BW can vary as much as 100-fold between breeds (Burger 1994). Another format, body surface area (BSA) dosing format, which is given in terms of mg/m², is advantageous in some situations because the metabolic rate is proportional to BSA (Edelbi et al. 2012) though most drugs are prescribed in mg/kg on a BW basis in veterinary medicine. In practice, veterinarians treating large-breed dogs frequently prescribe PDS at a lower dose than that calculated on a BW basis or empirically because these calculations overestimate the dose required for large...
dogs. This study was designed to evaluate the gaps in pharmacokinetic (PK) profiles from two dosing formats of PDS (BW versus BSA formula) in small- and large-breed dogs.

**Materials and Methods**

Pure PDS powder (Sigma Aldrich, St. Louis, MO, U.S.A.) and PDS tablets (Sorondo, Yuhan Corporation, Seoul, Korea) were used. Methanol (MS1922-001) and acetonitrile (AS1122-001) were of high-performance liquid chromatography (HPLC) grade and were purchased from Avantor™ (Center Valley, PA, U.S.A.).

Fifteen healthy dogs were assigned to three groups; group A consisted of 5 beagles (2 females and 3 males), aged 3-5 years, with a BW of 9.9±1.7 kg. Groups B and C consisted of 10 large mixed-breed dogs (7 females and 3 males; 5 per group), aged 3-4 years, with a BW of 29.0±2.9 kg. All dogs were healthy based on physical examinations and basic screening tests. This study was conducted in accordance with the Guide for the Care and Use of Laboratory Animals, and was approved by Chungnam National University (CNU-00520, 11, Dec, 2014).
Groups A and B received 2 mg/kg of oral PDS with a Greenies Pill Pocket (The Nutro Company, TN, U.S.A) twice daily for one week. Group C received 40 mg/m² (about 1.3 mg/kg) of oral PDS twice daily for one week. BSA (m²) was estimated using the formula \[10.1 \times \text{BW (kg)}^{0.73}/10^2\]. These doses were based on current recommendations for BW- and BSA based dosing (Plumb 2011, Withrow et al. 2013).

Venous blood samples (2 ml) were collected from the jugular veins of each dog at 0, 0.25, 0.5, 1, 1.5, 2, 4, 8, and 12 hr after dosing on day 7. Samples were immediately centrifuged and stored at -80°C. Plasma PDS levels were determined using HPLC-tandem mass spectrometry. Plasma concentration-time profiles were analysed using non-compartment analysis with WinNonlin 4.1 (Pharsight Corporation, Princeton, NJ, U.S.A.) to obtain PK parameters for each animal. One-way ANOVA was used to investigate associations among the three groups using SPSS 21.0.0 (SPSS Inc., Chicago, IL, U.S.A.).

Results and Discussion

None of the dogs had severe systemic adverse effects during the 7-day treatment period or during the following 14 days. Figure 1 shows the plasma concentration-time profiles for the three groups. The PK parameters including the maximum concentration (C_{max}), time to C_{max} (T_{max}), and area under the curve (AUC) are detailed in Table 1. T_{max} was similar among the 3 groups (0.9, 1.1, and 0.8 hr, respectively). C_{max} and AUC were significantly greater in group B (1918.00 ng/ml and 5597.79 ng · hr/ml) than in group A (777.2 ng/ml and 2074.59 ng · hr/ml) and group C (427.80 ng/ml and 1428.79 ng · hr/ml).

There have been several previous PK studies of PDS in dogs. One study reported PK parameters at a single administration of PDS (1 mg/kg) to beagles (Van der Heyden et al. 2012) and another study investigated PK parameters at doses of 5 mg and 30 mg (Colburn and Buller 1973, Tse and Welling 1977). In humans, a clinical oral dosing of PDS at 25 mg to 60 mg, were studied (Lee 1991, Mollmann et al. 1995). The values previously reported for T_{max} in the veterinary and human studies are generally similar to those in the present study; however, dose normalized C_{max}, and AUC were quite different between studies. Group C was administered an approximately 1.54 fold lower dose of PDS than those of group B, while group B showed an approximately 4 fold higher exposure (e.g. C_{max} and AUC) than group C. This discrepancy between dose and exposure level seemed to result from metabolic saturation and/or breed related differences.

Based on this pilot study, BW-based dosing of oral PDS yielded higher blood concentrations of PDS than BSA-based dosing in large-breed dogs. Dose normalized C_{max} and AUC were similar between small breed dogs given 2 mg/kg and large-breed dogs given 40 mg/m². Further studies are needed to identify a BSA-based canine dose of prednisolone that will yield PK results similar to those observed using the BW-based dose with chronic toxicity or cumulative adverse effects in small and large-breed dogs.

References