Polish Journal of Veterinary Sciences Vol. 20, No. 3 (2017), 611–613

DOI 10.1515/pjvs-2017-0076

Short communication

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

A. Nam[1*], S.M. Kim[2*], J.W. Jeong[3], K.H. Song[2], T.S. Koo[3*], K.W. Seo[2*]

[1] Department of Veterinary Internal Medicine, College of Veterinary Medicine, Seoul National University, Seoul 08826, Republic of Korea
[2] Laboratory of Veterinary Internal Medicine, College of Veterinary Medicine, Chungnam National University, Daejeon 34134, Republic of Korea
[3] Graduate School of New Drug Discovery and Development, Chungnam National University, Daejeon 34134, Republic of Korea

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/m^2. 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/m^2, 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

Correspondence to: K.W. Seo, e-mail: kwseo@cnu.ac.kr, T.S. Koo, e-mail: kootae@cnu.ac.kr

* These authors contributed equally to this study.

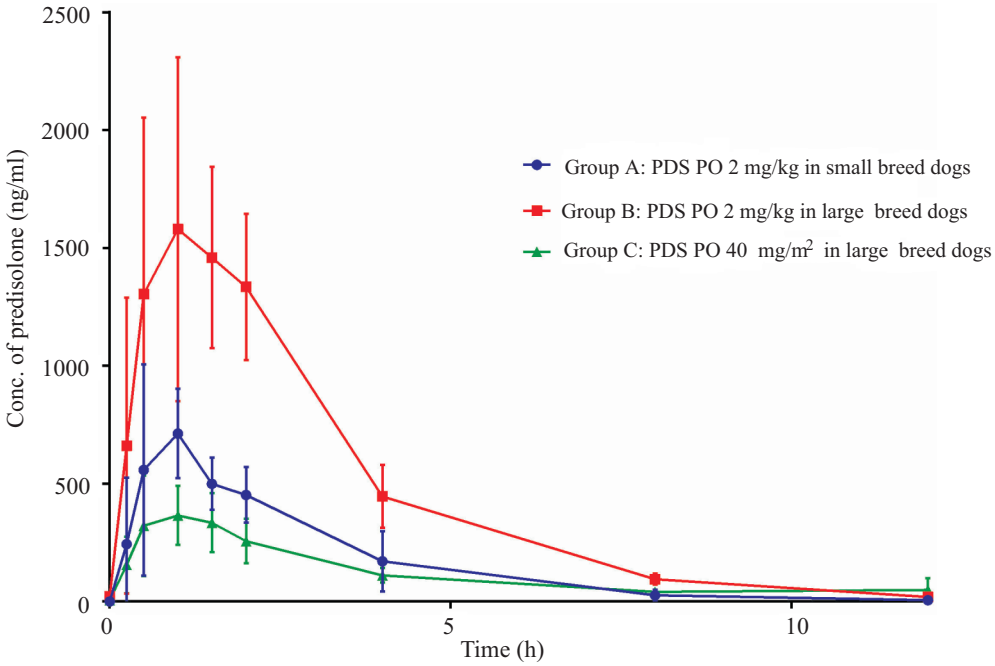

Fig. 1. Plasma concentration-time profiles of prednisolone following oral administration to small-breed dogs (Group A) and large-breed dogs (Group B and Group C).

Table 1. Pharmacokinetic parameters (Mean ± SD) of prednisolone after oral administration of 2 mg/kg in Beagles (Group A), large breed dogs (Group B) and 40 mg/m^2 (about 1.3 mg/kg) in large breed dogs (Group C).

Pharmacokinetic parameters	Group A (n = 5)	Group B (n = 5)	Group C (n = 5)
	PDS PO 2 mg/kg in small breed dogs	PDS PO 2 mg/kg in large breed dogs	PDS PO 40 mg/m in large breed dogs
T_{max} (hr)	0.90 ± 0.42	1.10 ± 0.55	0.80 ± 0.45
C_{max} (ng/ml)	777.20 ± 258.01	1918.00 ± 305.97[a]	427.80 ± 99.40[b]
$T_{1/2kel}$ (hr)	1.46 ± 0.24	1.79 ± 0.35	3.22 ± 0.62
AUC_{last} (ng · hr/ml)	2074.59 ± 416.00	5597.79 ± 984.08[a]	1428.79 ± 448.27[c]
AUC_{inf} (ng · hr/ml)	2090.31 ± 417.75	5650.44 ± 987.70	1690.72 ± 680.60

T_{max} = Time until maximum concentration. C_{max} = Maximum concentration. $T_{1/2kel}$ = Terminal elimination half-life. AUC_{last} = Area under the plasma concentration-time curve from time zero to time of last measurable concentration. AUC_{inf} = Area under the plasma concentration-time curve from time zero to infinity.
[a] Significantly greater compared with group A and C (P<.01 for both comparisons)
[b] No significant difference compared with group A (p=0.091)
[c] No significant difference compared with group A (p=0.314)

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/m^2 (about 1.3 mg/kg) of oral PDS twice daily for one week. BSA (m^2) was estimated using the formula [10.1 × BW (kg)$^{2/3}$]/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/m^2. 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

Burger IH (**1994**) Energy needs of companion animals: matching food intakes to requirements throughout the life cycle. J Nutr 124 (Suppl 12): 2584S-2593S.

Colburn WA, Buller RH (**1973**) Radioimmunoassay for prednisolone. Steroids 21: 833-846.

El Edelbi R, Lindemalm S, Eksborg S (**2012**) Estimation of body surface area in various childhood ages – validation of the Mosteller formula. Acta Paediatr 101: 540-544.

Lee KH (**1991**) Bioavailability of oral prednisolone. Seoul J Med 32: 131-137.

Mollmann H, Hochhaus G, Rohatagi S, Barth J, Derendorf H (**1995**) Pharmacokinetic/pharmacodynamic evaluation of deflazacort in comparison to methylprednisolone and prednisolone. Pharm Res 12: 1096-1100.

Plumb DC (**2011**) Plumb's veterinary drug handbook. 7th ed., Wiley Blackwell, Stockholm, WI.

Tse FL, Welling PG (**1977**) Prednisolone bioavailability in the dog. J Pharm Sci 66: 1751-1754.

Van der Heyden S, Croubels S, Gadeyne C, Ducatelle R, Daminet S, Murua Escobar H, Sterenczak K, Polis I, Schauvliege S, Hesta M, Chiers K (**2012**) Influence of P-glycoprotein modulation on plasma concentrations and pharmacokinetics of orally administered prednisolone in dogs. Am J Vet Res 73: 900-907.

Withrow SJ, Vail DM, Page R (**2013**) Withrow and MacEwen's small animal clinical oncology. 5th ed., Elsevier Saunders, St. Louis, MO.