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Comparative Serum Prednisone and Prednisolone Concentrations following Prednisone or Prednisolone Administration to Beagle Dogs

W. A. COLBURN *, C. R. SIBLEY, and R. H. BULLER ˣ

Abstract □ The relative serum prednisone and prednisolone concentrations were determined following the administration of prednisone or prednisolone as 5-mg tablets to male beagle dogs. Serum prednisone concentrations were significantly greater following prednisone administration than they were following prednisolone administration. Serum prednisolone concentrations were significantly greater following treatment with prednisolone than with prednisone. The combined prednisone and prednisolone areas under the serum concentration–time curves were similar for the two treatments.

Keyphrases □ Prednisone—serum concentration after administration of prednisone or prednisolone, radioimmunoassay, dogs □ Prednisolone—serum concentration after administration of prednisolone or prednisone, radioimmunoassay, dogs □ Bioavailability—prednisone and prednisolone, serum radioimmunoassay, dogs □ Glucocorticoids—prednisone and prednisolone, serum radioimmunoassay, dogs

With the advent of radioimmunoassays for both prednisone and prednisolone (1, 2), a unique opportunity arose to investigate the interconversion of prednisone and prednisolone in many experimental animals and in humans. In the present study, male beagle dogs were chosen as the test animal.

Previously, the conversion and interconversion of prednisone and prednisolone had been studied by tedious, time-consuming, and often difficult methods (3–7). With radioimmunoassays, the analyses could be conducted in just days without chromatography or separation steps.

The present study was conducted to investigate the interconversion of prednisone and prednisolone following the administration of 5-mg compressed tablets of prednisone[1] or prednisolone[2] to male beagle dogs.

EXPERIMENTAL

Materials—The buffers used were: tromethamine, 0.2 *M* and pH 8.0 (I), and sodium phosphate (monobasic and dibasic), 0.2 *M* and pH 6.5 (II). The tritiated steroids[3] were 6,7-^{3}H-prednisone at 40.0 Ci/mmole and 6,7-^{3}H-prednisolone at 45.4 Ci/mmole. The primary antiserums were rabbit antiprednisolone 21-hemisuccinate–bovine serum albumin (III) and rabbit antiprednisone 21-hemisuccinate–bovine serum albumin (IV).

Goat antirabbit serum or ammonium sulfate solution (80% saturated) was used as the precipitant. Analytical grade toluene-based liquid scintillation counting solution[3,4] was used, and the high capacity liquid scintillation spectrophotometer had a 4° refrigeration unit[5]. Other materials consisted of 1-ml adjustable automatic pipets and 100-, 200-, and 500-μl pipets with disposable tips[6,7]; 7-ml glass disposable miniature liquid scintillation counting vials with glass minivial holders[8]; 10 × 75-mm disposable culture tubes[9]; and a moderate speed refrigerated centrifuge[10].

Methods—*Animal Study*—Sixteen male beagle dogs, 9.5–17.2 kg, were placed in a randomized two-way crossover design. Blood samples were withdrawn from the jugular vein immediately prior to drug ad-

[1] Deltasone, 5-mg compressed tablet, The Upjohn Co.
[2] Delta-Cortef, 5-mg compressed tablet, The Upjohn Co.
[3] Bio-Solv, Beckman Instrument Co.
[4] Liquifluor, New England Nuclear Corp.
[5] Model 2450 Tri-Carb liquid scintillation spectrophotometer, Packard Instrument Co.
[6] Biopette, Bioschwartz.
[7] Microliter pipets, Eppendorf.
[8] Miniature holder and vials, Demuth Glass Co.
[9] Disposable culture tubes, Kimble Glass Co.
[10] Refrigerated centrifuge, International Equipment Co.

Table I—Quantity (Milliliters) of Solutions in Prednisolone Assay Tubes

	Total Count	Zero Control	Standard	Unknowns	References
Buffer	0.6	0.1	—	0.1	—
Standard in buffer	—	—	0.1	—	0.1
Antiprednisolone	—	0.5	0.5	0.5	0.5
^{3}H-Prednisolone	0.2	0.2	0.2	0.2	0.2
Blank dog serum	0.1	0.1	0.1	—	0.1
Unknown dog serum	—	—	—	0.1	—
Antirabbit serum	0.1	0.1	0.1	0.1	0.1
Totals	1.0	1.0	1.0	1.0	1.0

Table II—Quantity (Milliliters) of Solutions in Prednisone Assay Tubes

	Total Count	Zero Control	Standard	Unknowns	References
Buffer	0.2	0.1	—	0.1	—
Standard in buffer	—	—	0.1	—	0.1
Antiprednisone	—	0.1	0.1	0.1	0.1
^{3}H-Prednisone	0.2	0.2	0.2	0.2	0.2
Blank dog serum	0.1	0.1	0.1	—	0.1
Unknown dog serum	—	—	—	0.1	—
Ammonium sulfate	0.6	0.6	0.6	0.6	0.6
Totals	1.1	1.1	1.1	1.1	1.1

ministration and at 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 hr after drug administration. Samples were allowed to clot for 45 min and then were centrifuged for 20 min. The serum layer was removed, placed in labeled tubes, and frozen at −20° until analysis.

The treatments used were designated: A, prednisolone, 5-mg tablet; and B, prednisone, 5-mg tablet. Eight dogs received prednisolone during the 1st week of the study and prednisone during the 2nd week. The eight dogs in the other group received the drugs in reverse order.

Prednisolone Assay—Prednisolone antiserum stock solution was stored frozen at 1:10 dilution in tromethamine buffer. A final dilution of 1:650 was used in the assay. Standard prednisolone[11] was used to prepare known concentrations of 0.5–128 ng/ml of the tromethamine buffer. The 12-ng/ml standard was used to maintain a reference control throughout the analyses. All standards were stored in screw-capped[12] vials at 4°. Goat antirabbit serum was used at a final dilution of 1:4 to precipitate the primary antibody. Dog serum samples were diluted 1:10 before analysis by radioimmunoassay.

In the specific analytical procedure, 10 × 75-mm glass disposable culture tubes were labeled for controls, standards, and unknown samples. One-half milliliter of the tromethamine buffer was added to the total radiation tubes while antiprednisolone was added to the standard, zero-control, reference, and unknown tubes. Then 0.1 ml of the tromethamine buffer was added to the total radiation, zero-control, and unknown sample tubes while 0.1 ml of diluted blank serum was added to the zero-control, total radiation, reference, and standard tubes.

The standard and reference tubes received 0.1 ml of the respective standard solutions ranging from 0.5 to 128 ng/ml. One-tenth-milliliter aliquots of the unknown samples were placed in the respective assay tubes. All assay tubes received 0.2 ml (5000 counts/min) of ^{3}H-prednisolone; then they were agitated and allowed to equilibrate for 2 hr at room temperature. One-tenth milliliter of appropriately diluted goat antirabbit serum was added to every assay tube. All tubes were again agitated and allowed to equilibrate overnight at 4°. The volumes of the solutions in each tube are listed in Table I.

Approximately 16 hr later, all tubes were centrifuged at 2000 rpm; 0.6 ml of the supernate (unbound fraction) was aspirated and placed in a minivial containing 5 ml of liquid scintillation counting solution. These samples were counted for 5 min in a suitable multiple-sample liquid scintillation spectrophotometer with the refrigeration unit set at 4°. Standard concentrations were plotted semilogarithmically, and the unknown concentrations were determined by interpolation from the maximum slope. The establishment of the standard curve and interpolation of results were accomplished by a computer program[13].

Prednisone Assay—Prednisone antiserum stock solution was stored at −20° at a dilution of 1:10 in the sodium phosphate buffer. A dilution of 1:100 was prepared immediately prior to use in the assay. Prednisone[14] was used to prepare standard concentrations ranging from 0.13 to 48 ng/ml in the sodium phosphate buffer. The 2-ng/ml standard was used as a reference standard throughout the analyses.

All standards were stored in screw-capped[12] vials at 4°. An 80% saturated ammonium sulfate solution was used to precipitate the primary antibody–antigen complex. The same dog serum samples that had been diluted 1:10 for the prednisolone assay were used in the prednisone assay.

Duplicate 10 × 75-mm glass disposable culture tubes were labeled for zero-control, reference standard, standard control, unknown sample, and total radiation tubes. Total radiation, zero-control, and unknown serum sample tubes received 0.1 ml of the sodium phosphate buffer, while the standard and reference tubes received 0.1 ml of their respective standard prednisone concentrations in this buffer. One-tenth-milliliter aliquots of diluted blank dog serum were added to all assay tubes except the unknown sample tubes; 0.1 ml of the diluted unknown dog serum was used in the unknown sample tubes. One-tenth milliliter of appropriately diluted antiprednisone serum was placed in all assay tubes except those labeled for total radiation, and the total radiation tubes received 0.1 ml of the sodium phosphate buffer.

All tubes received 0.2 ml of the sodium phosphate buffer containing 4000 cpm of ^{3}H-prednisone. All assay tubes were allowed to equilibrate for 2 hr at room temperature before 0.6 ml of 80% saturated ammonium sulfate solution was added. The tubes were allowed to incubate overnight at 4°. The total volumes of each solution in the tubes are given in Table II.

After about 16 hr, all tubes were centrifuged at 3000 rpm for 20 min at 4°. A 0.6-ml aliquot of the supernate (unbound fraction) was placed in a minivial containing 5 ml of counting solution. All vials were counted in a suitable liquid scintillation spectrophotometer for one 5-min period. Standard concentrations were plotted semilogarithmically, and the unknown serum sample concentrations were determined by interpolation from the standard curve. The plotting of the standard curve and interpolation of the unknown sample results were accomplished by a computer program[15].

RESULTS

All dog serum samples were collected and stored according to protocol. Prednisolone and prednisone assays were carried out on each

Table III—Physicochemical Parameters

Parameter	Prednisolone, 5-mg Compressed Tablet	Prednisone, 5-mg Compressed Tablet
Dissolution rate, T_{50}, min		
Mean	4.4	6.5
High	5.6	8.6
Low	3.8	5.5
Disintegration rate, T_{50}, min		
Mean	1.5	3.5
High	2.0	4.0
Low	1.0	2.3
Content uniformity, %		
Mean	99.2	99.5
High	103.8	102.4
Low	94.4	98.0

[11] Control reference standard prednisolone, The Upjohn Co.
[12] Lined with Teflon (du Pont).
[13] Curve-fitting and interpolating computer program, A. R. Lewis, The Upjohn Co.
[14] Control reference standard prednisone, The Upjohn Co.
[15] Computer program, A. R. Lewis, The Upjohn Co.

Table IV—Summary of Prednisolone Bioavailability Data

		Prednisolone, 5-mg Compressed Tablet (A)	Prednisone, 5-mg Compressed Tablet (B)	Statistically Significant Difference, Tukey's, $p < 0.05$
	Hours	Serum Levels, ng/ml		
Serum concentration, ng/ml, by hourly intervals	0.5	204	139	A > B
	1	242	205	N.S.[a]
	2	196	184	N.S.
	3	156	136	N.S.
	4	104	93	N.S.
	6	46	41	N.S.
	8	20	18	N.S.
	12	4	3	N.S.
	24	0	0	N.S.
Mean area under serum concentration–time curve, ng/ml × hr		986	855	A > B
Peak of mean serum concentration, ng/ml		242	205	N.S.
Mean individual peak serum concentration, ng/ml		273	234	N.S.
Mean peak time, hr		0.9	1.3	N.S.
Half-lives, hr		1.8	1.6	N.S.

[a] N.S. = not significant.

sample. The relative bioavailability of one lot of prednisolone and one lot of prednisone was determined by comparing mean areas under the serum concentration–time curves, mean peak serum concentrations, and mean times of the peak serum concentrations as well as other relevant parameters. The two lots were compared for prednisolone concentrations, prednisone concentrations, and combined concentrations. The physicochemical parameters of the two treatments, 5-mg prednisolone tablets and 5-mg prednisone tablets, are given in Table III.

Significantly different serum concentrations were observed in the early portions of the serum concentration–time curves. The prednisolone treatment was significantly greater than the prednisone treatment according to the prednisolone levels at 0.5 hr (Table IV). The prednisolone treatment was significantly less than the prednisone treatment at the 1- and 2-hr intervals according to the prednisone concentrations (Table V). The combined serum steroid levels were not statistically different throughout the blood level curves (Table VI).

The mean areas under the serum prednisolone concentration–time curves were 986 and 855 ng/ml × hr (Table IV and Fig. 1), the prednisone areas were 638 and 694 ng/ml × hr (Table V and Fig. 2), and the combined areas were 1624 and 1550 ng/ml × hr (Table VI and Fig. 3) for the prednisolone and prednisone treatments, respectively. There were statistically significant differences between the two treatments according to prednisone and prednisolone concentrations; but according to the combined areas, the two treatments were not statistically different.

Following prednisolone administration, the serum prednisolone levels were significantly greater than they were following prednisone administration. Serum prednisone levels were significantly greater following prednisone administration than they were following prednisolone administration. However, when comparing the combined areas under the serum concentration–time curves for the two steroids, no statistically significant differences were observed.

Mean peak serum prednisolone concentrations were 242 and 205 ng/ml (Table IV and Fig. 1) for the prednisolone and prednisone treatments, respectively. Mean peak concentrations were attained at 0.9 and 1.3 hr (Table IV) for the two treatments. Mean peak prednisone concentrations were 111 and 132 ng/ml for the prednisolone and prednisone treatments (Fig. 2), while peaks were attained

Table V—Summary of Prednisone Bioavailability Data

		Prednisolone, 5-mg Compressed Tablet (A)	Prednisone, 5-mg Compressed Tablet (B)	Statistically Significant Difference, Tukey's $p < 0.05$
	Hours	Serum Levels, ng/ml		
Serum concentration, ng/ml, by hourly intervals	0.5	53	74	N.S.[a]
	1	96	131	A < B
	2	111	132	A < B
	3	100	105	N.S.
	4	78	82	N.S.
	6	45	40	N.S.
	8	22	21	N.S.
	12	6	6	N.S.
	24	0	0	N.S.
Mean area under serum concentration–time curve, ng/ml × hr		638	694	A < B
Peak of mean serum concentration, ng/ml		111	132	A < B
Mean individual peak serum concentration, ng/ml		124	149	A < B
Mean peak time, hr		2.0	1.2	A > B
Half-lives, hr		2.2	2.3	N.S.

[a] N.S. = not significant.

Table VI—Combined Steroid Bioavailability Data Summary[a]

		Prednisolone, 5-mg Compressed Tablet	Prednisone, 5-mg Compressed Tablet
	Hours	Serum Levels, ng/ml	
Serum concentration, ng/ml, by hourly intervals	0.5	257	213
	1	338	336
	2	307	316
	3	256	241
	4	182	175
	6	91	81
	8	42	39
	12	10	9
	24	0	0
Mean area under serum concentration–time curve, ng/ml × hr		1624	1550
Peak of mean serum concentration, ng/ml		338	336
Mean individual peak serum concentration, ng/ml		397	383
Mean peak time, hr		1.5	1.3
Half-lives, hr		2.0	1.9

[a] Differences were not significantly different according to the Tukey test at the $p < 0.05$ level.

at 2.0 and 1.2 hr, respectively. Peak serum prednisone concentrations and times were significantly different according to Tukey's method of comparison. Mean peak combined concentrations were 338 and 336 ng/ml (Table VI) and peak times were 1.5 and 1.3 hr for the prednisolone and prednisone treatments, respectively.

The means of the individual peak concentrations were 273 and 234 ng/ml for prednisolone (Table IV), 124 and 149 ng/ml for prednisone (Table V), and 397 and 383 ng/ml for the combined levels for the prednisolone and prednisone treatments, respectively. The two values from the prednisone treatment were significantly different by Tukey's method of analysis.

No statistically significant differences for the half-lives were detected between the treatments. The half-lives were 1.8 and 1.6 hr for prednisolone (Table IV) and 2.2 and 2.3 hr for prednisone (Table V) for the prednisolone and prednisone treatments, respectively.

The areas under the serum prednisone concentration–time curves were only 65% as large as the serum prednisolone concentration–time curve areas for the prednisolone treatment. Concurrently, the serum prednisone concentration areas were 81% as large as the prednisolone areas under the curve for the prednisone treatment. The prednisone areas under the serum level curves were 87% as large for the prednisolone treatment as for the prednisone treatment. At the same time, the areas under the serum prednisolone concentration–time curves were 92% as great for the prednisone treatment as for the prednisolone treatment. The areas under the curves for prednisone were 28% less than the simultaneous prednisolone areas throughout the study. The combined steroid areas under the curves were 95% as large for the prednisone treatment as for the prednisolone treatment.

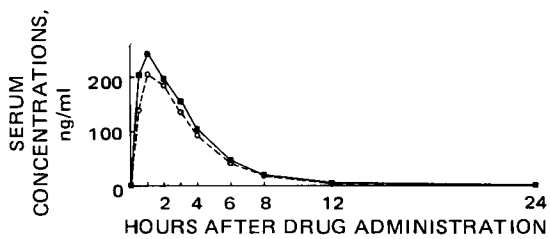

Figure 1—*Serum prednisolone concentration–time curves following oral administration of 5 mg of prednisolone (■) or prednisone (O) to 16 male beagle dogs.*

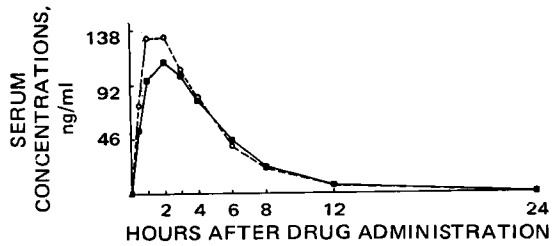

Figure 2—*Serum prednisone concentration–time curves following oral administration of 5 mg of prednisolone (■) or prednisone (O) to 16 male beagle dogs.*

DISCUSSION

The bioavailability, interconversion rates, and metabolism of prednisone and prednisolone have long intrigued the scientific community (9–11). With the recent advent of radioimmunoassays for the quantitation of these two compounds in biological fluids, a unique opportunity became available. The preceding results were obtained using these two assay methods to establish the simultaneous serum prednisone and prednisolone concentrations in male beagle dogs following treatment with prednisone or prednisolone.

It is apparent from the hourly serum concentrations that the immediate availability of the drugs depends only slightly on which drug is administered, indicating that the biological interconversion is very rapid. However, in both cases, *i.e.*, serum prednisone and prednisolone concentrations, the predominant drug in the serum is the administered drug. The drug being administered reaches the circulatory system more quickly than does the major metabolite, even though the interconversion is rapid.

The areas under the serum concentration–time curves followed an identical pattern. Prednisolone areas under the curves were always greater than the concomitant prednisone areas, but the prednisone areas were greater following prednisone administration than they were following prednisolone treatment, and prednisolone areas were larger following prednisolone than they were following prednisone. The differences were statistically significant in both cases; but when the combined prednisone–prednisolone areas under the curves were compared, the areas were not significantly different between the two treatments.

Peak serum concentrations were approximately two times as great for prednisolone as they were for prednisone regardless of the treatment. Peak serum prednisone concentrations were significantly higher following prednisone administration than they were following prednisolone administration. The differences in peak serum prednisolone concentrations were not statistically different with respect to treatment, and the combined prednisone–prednisolone peak serum concentrations were essentially equal.

Although the area under the serum concentration–time curve for prednisone was only 13% less for the prednisolone treatment than for the prednisone treatment, the areas were significantly different according to Tukey's method of analysis. This result was possible be-

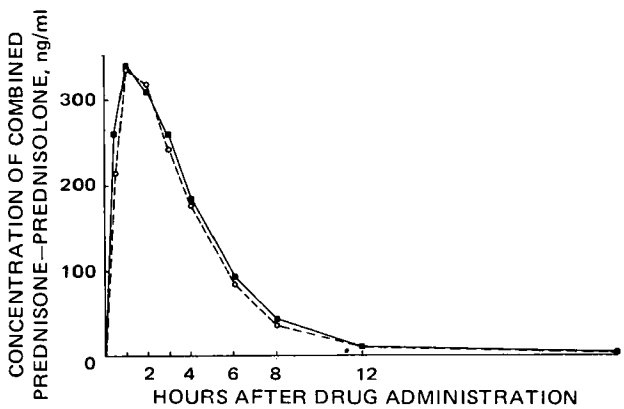

Figure 3—*Combined serum prednisolone and prednisone concentration–time curves. Key: ■, prednisolone treatment, and O prednisone treatment.*

cause of the extremely low overall coefficient of variation. The variation, including assay variation and intra- and intersubject variations, for the prednisone data was 15%. A statistically significant difference was found between the two treatments according to prednisolone data as well. Again, even though the observed difference was only 8% between the two treatments, significance was established and was attributed to the excessively low overall coefficient of variation (12%). The combined prednisone–prednisolone areas under the serum concentration–time curves were not different between the two treatments.

There was a consistent difference between treatments by both methods of analysis. However, the amount of synthetic steroid available following each treatment was essentially the same. Prednisolone was always present in larger quantities than was prednisone, regardless of the drug administered. The relative levels of prednisolone to prednisone, prednisolone to administered drug, and prednisone to administered drug in serum were dependent on which drug was administered. Contrary to previously published studies (8–11), prednisone areas under the serum concentration–time curves were greater following prednisone administration than they were after prednisolone administration, while prednisolone areas were greater following prednisolone treatment than they were following prednisone administration. The predominating steroid in serum was prednisolone, even though the relative serum levels were dependent on the administered drug.

Although there were statistically significant differences under the serum concentration–time curves between the two treatments, the therapeutic significance is difficult to assess. Both of these anti-inflammatory steroids are used on a chronic multiple-dose basis. The clinician establishes the dosing regimen by titrating the dose to a therapeutic end-point, *i.e.*, remission of symptoms. Even if these results were confirmed in humans, it would be difficult to establish that an 8 or 13% difference in total area under the serum concentration–time curve would actually be significant in the clinical situation.

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Nonlinear Pharmacokinetic Model of Intravenous Anesthesia

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Abstract □ A nonlinear pharmacokinetic model was constructed to describe the body distribution of intravenous anesthetics, using the physiological modeling approach for drug distribution kinetics. The model considers the physiological parameters of tissue volumes and blood flow rates for the standard four phases of blood, viscera, lean tissue, and adipose tissue and also the associated drug parameters known to influence drug distribution. A simple ramp function having a characteristic time (volume per flow rate) is used to describe the rate of approach to equilibrium conditions for each tissue phase. The model was evaluated for the distribution of methohexital and thiopental by comparing calculated values to experimental drug concentrations taken from the literature. The physiological alteration of obesity also was programmed into the model to evaluate its capability for predicting the influence of body alterations on drug distribution. The results indicated that a preliminary mathematical model of relatively simple design is capable of at least a semiquantitative prediction of intravenous anesthetic drug concentrations in body tissues and has the potential of accounting for differences in drug distribution in the presence of selected physiological alterations.

Keyphrases □ Anesthesia, intravenous—distribution, nonlinear pharmacokinetic model described, methohexital and thiopental □ Pharmacokinetic models, nonlinear—described for intravenous anesthetics methohexital and thiopental □ Distribution, drug—intravenous anesthesia, nonlinear pharmacokinetic model described

Induction, maintenance, and recovery during intravenous anesthesia are dependent upon the amounts of anesthetic agent within the brain tissues after dosing and are functions of the amounts of drug in the plasma. Alterations in body distribution processes controlling drug levels in the brain and plasma can influence the dosages required for anesthesia and may explain many ineffective dose regimens for these drugs.

Clinical use of methohexital and thiopental for anesthesia in dental patients has indicated some conditions that can alter the tissue levels of these anesthetics to result in enhanced potency or prolonged narcosis after normal induction doses. These conditions include dehydration (1), uremia (2), peripheral circulatory failure (2), increased cardiac output (2), electrolyte disturbances (2), hepatic failure (2), and chronic renal failure (3).

Attempts have been made to describe the pharma-