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# Comparative Bioavailability: Eight Commercial Prednisone Tablets

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*Two four-treatment crossover bioavailability studies were performed in panels of 12 adult male volunteers with eight different commercial prednisone tablets. Plasma samples from the first study were assayed by radioimmunoassay for both prednisone and prednisolone. Plasma samples from the second study were assayed for prednisolone only. Statistical analyses of the data showed significant differences in the rate of appearance of prednisolone in plasma, but not in the amount converted to prednisolone. Some observations are made on the relationships between prednisone and prednisolone concentrations in plasma following oral administration of prednisone.*

**KEY WORDS:** prednisone bioavailability; elimination half-lives of prednisone and prednisolone; prednisone and prednisolone plasma levels following prednisone.

## INTRODUCTION

With the development of radioimmunoassays for prednisone (1) and its metabolite, prednisolone (2), it is now possible to measure the plasma levels of these steroids following the oral administration of a single, low dose of prednisone. The early observations, of Campagna *et al.* (3) and Levy *et al.* (4) demonstrated a potential bioavailability problem with prednisone tablets which only recently could begin to be assessed. Two earlier papers (5,6)

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reported data on some prednisone tablets. One of these (6) reported results of our first prednisone study.

It is well documented that prednisone is metabolized to prednisolone (7–9), which is assumed to be its active form. However, in most of these studies the metabolites of prednisolone have been isolated only from urine, or plasma levels of prednisolone have been measured following high doses of prednisone. In only one unpublished study of DiSanto *et al.* has the determination of both prednisone and prednisolone in plasma been undertaken.

This article reports the results of two four-treatment crossover studies with commercially available prednisone tablets. In the second prednisone study both prednisone and prednisolone plasma levels were measured, while in the third prednisone study only prednisolone was measured in plasma. All tablets utilized in the studies were purchased on the open market by the Food and Drug Administration.

## EXPERIMENTAL

### *In Vitro* Studies

Dissolution testing was performed in the laboratories of the Food and Drug Administration according to the specifications of the USP XVIII. Results of dissolution rate tests on the same tablets by another method will be reported in a subsequent publication.

### Subjects

Twelve adult male volunteers between the ages of 21 and 32 years, weighing between 60.3 and 82.6 kg and in good health, were selected for each study. Six of the subjects participated in both studies. Each subject received a medical history, physical examination, and blood and urine analysis including plasma 17-OHCS.

All subjects selected received no barbiturates or other enzyme-inducing agents for a period of 30 days preceding the study until its completion. They received no other medication or alcoholic beverages for a period beginning 7 days preceding the study until completion of the study. The subjects were assigned numbers which were ordered according to increasing body weight.

### Study Conditions

Subjects fasted overnight (from 10 P.M.) until 4 hr after administration of each dose of prednisone. On the mornings when medication was administered, each subject drank 240 ml of water within the first hour after

arising. From 4 hr after dosing with prednisone, food and beverage were taken *ad libitum*.

## Blood Sampling

Fifty milliliters of whole blood was taken from a forearm vein just before dosing with prednisone at 0 time, and 12 ml (Study 2) or 10 ml (Study 3) of whole blood was taken at 0.25, 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 hr after dosing with prednisone. The blood samples were drawn into Vacutainer tubes containing heparin as the anticoagulant. Each sample of blood was centrifuged as soon as possible after collection and the plasma was placed in one vial, stoppered, and labeled immediately. The plasma samples were then quick frozen, and stored in the frozen state until just prior to assay.

## Treatments and Schedules

At 11 P.M. on the day before each treatment period, each subject took 1.0 mg of dexamethasone orally to suppress the endogenous secretion of cortisol. At 8 hr after prednisone administration, each subject took 0.5 mg of dexamethasone orally to maintain the suppression.

On each phase of Study 2, each subject ingested 10 mg of prednisone as two 5-mg tablets N, D, U, or R.[4] The tablets were taken in the morning (about 8 A.M.) with 180 ml of water. Treatments were separated by a 1-week period.

[4]Tablet N was prednisone, 5 mg (Nysco Laboratories), lot No. 49571; tablet D was prednisone, 5 mg (Danbury Pharmacal, Inc.), lot No. 4539; tablet U was Deltasone, 5 mg (Upjohn Co.), lot No. 786AEFI; tablet R was prednisone, 5 mg (Rexall Drug Co.), lot No. E 11499.

**Table I.** Treatment Schedules

| | | | Time period | | | |
|---|---|---|---|---|---|---|
| Study | Subject | Group | Week I | Week II | Week III | Week IV |
| 2 | 1, 2, 3 | I | N | D | R | U |
| | 4, 5, 6 | II | D | U | N | R |
| | 7, 8, 9 | III | U | R | D | N |
| | 10, 11, 12 | IV | R | N | U | D |
| | 1, 2, 3 | I | L | B | S | Mc |
| | 4, 5, 6 | II | B | Mc | L | S |
| | 7, 8, 9 | III | Mc | S | B | L |
| | 10, 11, 12 | IV | S | L | Mc | B |

The same protocol was repeated during Study 3 when each subject ingested 10 mg of prednisone as two 5-mg tablets of L, B, Mc, or S.[5]

The treatment schedules are shown in Table I. Studies 2 and 3 were separated by a period of approximately 6 months.

### Assay of Plasma Samples

The plasma concentrations of prednisone and its metabolite, prednisolone, were determined independently in each plasma sample from Study 2. The plasma concentration of prednisolone was determined in each plasma sample from Study 3. Each compound was measured by a radioimmunoassay procedure. The radioimmunoassay procedure for prednisolone has been given previously (10).

The procedure of Colburn (1) for the radioimmunoassay of prednisone was modified as follows: One milliliter of diluted plasma was incubated at 37°C for 10 min with 10 $\mu$l (2700 cpm) of ethanolic $^3$H-prednisone solution and 20 $\mu$l of antiserum. This incubation was followed by a second incubation at 0°C for 10 min. Two milliliters of a cold, saturated aqueous solution of ammonium sulfate was added to each sample and the solutions were mixed thoroughly. Each sample was centrifuged for 20 min at 2000 rpm. Following centrifugation, 1 ml of supernate was transferred to a scintillation vial containing 10 ml of Unogel and the radioactivity was counted for 10 min.

Binding curves were prepared using 0, 0.05, 0.25, 0.505, 1.01, and 2.02 ng of prednisone. Because of the high sentivity of this procedure, plasma samples had to be diluted with phosphate-buffered saline (*p*H 7.4) to be within the range of the assay. A 1:100 dilution was commonly used, but a 1:20 dilution was required for some samples. Binding curves were prepared for dilutions which were similar to those of the samples to be assayed, using each subject's "zero hour" plasma.

All binding curves were fitted essentially perfectly to a triexponential equation with the NONLIN program using an IBM 360/67 computer. The concentration of prednisone in the experimental samples was then determined by an iterative program using a Hewlett-Packard 9100A calculator. This procedure is more accurate than reading the concentration by sight from a standard curve.

## RESULTS AND DISCUSSIONS

### *In Vitro* Studies

The results of the USP dissolution testing of the tablets studied as reported by the Food and Drug Administration are summarized in Table II.

[5]Tablet L was prednisone, 5 mg (Lemmon Pharmacal), lot No. 1382; tablet B was prednisone, 5 mg (Barr Laboratories), lot No. 4126111; tablet Mc was prednisone, 5 mg (McKesson Laboratories), lot No. 3K668; tablet S was Meticorten, 5 mg (Schering Corp.), lot No. 2ABB-804.

**Table II.** Summary of Results of USP Dissolution Test Performed on Prednisone Tablets

| | Percent dissolved in 20 min | | |
|---|---|---|---|
| Tablet | Average | SD | Range |
| N | 47.5 | 4.09 | 40.7–55.2 |
| D | 4.84 | 1.65 | 1.6–8.2 |
| U | 103 | 1.61 | 102–105 |
| R | 40.6 | 13.9 | 18.6–61.2 |
| L | 39.0 | 7.94 | 28.4–60.8 |
| B | 54.2 | 1.89 | 50.9–56.7 |
| Mc | 34.7 | 23.5 | 12.7–89.8 |
| S | 112 | 2.96 | 108–118 |

The USP dissolution test requires that at least 60% of the labeled amount of prednisone in a tablet be dissolved in 20 min in the USP apparatus. Of the eight commercial products tested, only tablets U and S met this requirement. Tablet D was the slowest-dissolving tablet, with an average of 4.84% of label dissolved in 20 min. The remaining tablets were of intermediate dissolution rates, with average percent of label dissolved in 20 min ranging between 34.7% and 54.2%. The Food and Drug Administration has reported to us that there were problems in reproducing results from one laboratory to another with these tablets using the USP dissolution test.

## Assay Methods

The cross-reactivity of the prednisone and prednisolone antiserum with various endogenous steroids has been reported (1,2). The major interferences that could be anticipated are the reactions of cortisone with the prednisone antiserum and of cortisol with the prednisolone antiserum. In order to maintain the specificity of the assay technique, dexamethasone was administered to suppress the secretion of endogenous cortisol (9,11). Dexamethasone does not bind to either the prednisone or the prednisolone antiserum.

## Plasma Levels of Prednisone in Study 2

Table III summarizes the results of Study 2 obtained by measurement of plasma levels of prednisone, and the statistical analyses of these data. Analysis of variance for crossover design (ANOVA) of plasma concentrations indicated highly significant treatment differences among average plasma concentrations of prednisone at all sampling times except 24 hr. Dunnett's multiple comparison procedure (12) was used to identify significant differences between pairs of tablet averages. Tablet U was selected as the "standard" tablet since only it met the USP dissolution requirements.

**Table III.** Summary of Results of Prednisone Study 2: Prednisone Plasma Concentrations

| Parameter | Treatment averages | | | | Probability (among treatment averages) | Dunnett's multiple comparison test ($p \leq 0.05$) | | |
|---|---|---|---|---|---|---|---|---|
| | U | N | R | D | | U vs. N | U vs. D | U vs. R |
| Plasma concentration (ng/ml) at | | | | | | | | |
| 0.25 hr | 21.6 | 7.82 | 3.83 | 1.35 | $p < 0.001$ | Sig.[a] | Sig. | Sig. |
| 0.5 | 44.2 | 23.4 | 16.9 | 11.9 | $p < 0.001$ | Sig. | Sig. | Sig. |
| 1 | 66.6 | 52.6 | 36.9 | 28.4 | $p < 0.001$ | Sig. | Sig. | Sig. |
| 2 | 78.5 | 57.7 | 55.1 | 57.3 | $p < 0.001$ | Sig. | Sig. | Sig. |
| 3 | 76.2 | 60.2 | 61.0 | 68.9 | $p < 0.001$ | Sig. | N.S.[b] | Sig. |
| 4 | 58.2 | 48.2 | 55.7 | 68.2 | $p < 0.001$ | Sig. | Sig. | N.S. |
| 6 | 39.8 | 31.1 | 33.6 | 48.5 | $p < 0.001$ | Sig. | Sig. | N.S. |
| 8 | 27.1 | 21.3 | 25.4 | 36.5 | $p < 0.001$ | N.S. | Sig. | N.S. |
| 12 | 12.6 | 10.1 | 10.3 | 16.9 | $p < 0.001$ | N.S. | N.S. | N.S. |
| 24 | 1.82 | 2.68 | 1.39 | 1.79 | N.S. ($p > 0.25$) | N.S. | N.S. | N.S. |
| Area 0–24 hr [(ng/ml) × hr] | 586 | 464 | 469 | 607 | $p < 0.001$ | Sig. | N.S. | Sig. |
| Area 0–12 hr [(ng/ml) × hr] | 500 | 387 | 399 | 495 | $p < 0.001$ | Sig. | N.S. | Sig. |
| Peak plasma concentration (ng/ml) | 80.8 | 62.4 | 65.2 | 73.6 | $p < 0.001$ | Sig. | N.S. | Sig. |
| Half-life (hr) | 3.60 | 3.77 | 3.44 | 3.56 | N.S. ($p > 0.25$) | N.S. | N.S. | N.S. |
| Time to peak plasma level (min) | 128 | 125 | 165 | 185 | $0.01 < p < 0.025$ | N.S. | Sig. | Sig. |

[a]Sig.: difference between treatment means is significant at $p \leq 0.05$.
[b]N.S.: difference between treatment means is not significant at the 5% level or less.

**Table IV.** Summary of Results of Prednisone Study 2: Prednisolone Plasma Concentrations

| Parameter | Treatment averages | | | | Probability (among treatment averages) | Dunnett's multiple comparison test ($p \leq 0.05$) | | |
|---|---|---|---|---|---|---|---|---|
| | U | N | R | D | | U vs. N | U vs. D | U vs. R |
| Plasma concentration (ng/ml) at | | | | | | | | |
| 0.25 hr | 65.7 | 52.3 | 27.5 | 0.44 | $0.001 < p < 0.005$ | N.S. | Sig.[a] | N.S.[b] |
| 0.5 | 164 | 162 | 113 | 22.0 | $p < 0.001$ | N.S. | Sig. | N.S. |
| 1 | 222 | 231 | 172 | 79.7 | $p < 0.001$ | N.S. | Sig. | N.S. |
| 2 | 218 | 196 | 186 | 174 | N.S. ($0.10 < p < 0.25$) | N.S. | N.S. | N.S. |
| 3 | 171 | 163 | 168 | 184 | N.S. ($p > 0.25$) | N.S. | N.S. | N.S. |
| 4 | 134 | 119 | 130 | 155 | $0.005 < p < 0.01$ | N.S. | N.S. | N.S. |
| 6 | 75.5 | 80.5 | 76.1 | 98.3 | $0.005 < p < 0.01$ | N.S. | Sig. | N.S. |
| 8 | 36.7 | 45.4 | 39.2 | 59.2 | $p < 0.001$ | N.S. | Sig. | N.S. |
| 12 | 13.6 | 19.2 | 14.4 | 28.3 | $p < 0.001$ | N.S. | Sig. | N.S. |
| 24 | 1.13 | 3.83 | 0.57 | 2.25 | $0.025 < p < 0.05$ | N.S. | N.S. | N.S. |
| Area 0–24 hr [(ng/ml) × hr] | 1210 | 1258 | 1116 | 1273 | $0.025 < p < 0.05$ | N.S. | N.S. | N.S. |
| Area 0–12 hr [(ng/ml) × hr] | 1122 | 1120 | 1026 | 1090 | N.S. ($p > 0.25$) | N.S. | N.S. | N.S. |
| Peak plasma concentration (ng/ml) | 238 | 239 | 214 | 198 | $0.025 < p < 0.05$ | N.S. | N.S. | N.S. |
| Half-life (hr) | 2.36 | 2.95 | 2.99 | 3.40 | N.S. ($0.05 < p < 0.10$) | N.S. | N.S. | N.S. |
| Time to peak plasma level (min) | 75.0 | 70.2 | 107 | 155 | $p < 0.001$ | N.S. | Sig. | N.S. |

[a]Sig.: difference between treatment means is significant at $p \leq 0.05$.
[b]N.S.: difference between treatment means is not significant at the 5% level or less.

Again significant differences between average plasma concentrations were seen following tablet U compared to each of the other tablets up to approximately 8 hr after administration.

Average area (both 0–12 and 0–24 hr), average peak plasma concentration, and average time to reach peak plasma concentration demonstrated significant differences among tablets. The differences between average areas and average peak plasma concentrations remained significant when tablet U was compared with tablets N and R, but not when compared with tablet D. The difference between average time to reach peak plasma concentration was not significant when tablet U was compared with tablet N, but was significant in the cases when tablet U was compared with tablet D or R.

The coefficients of variation of the averages given in Table III are given in Table X.

### Plasma Levels of Prednisolone in Study 2

Table IV summarizes the results obtained when plasma concentrations of prednisolone were measured in Study 2 and the table also gives results of statistical analyses of these data by ANOVA. Significant differences among tablet average plasma concentrations at each sampling time, except 2 and 3 hr, were found. The differences between tablet averages were significant only when tablet U was compared with tablet D. There were no significant differences between tablet average plasma concentrations when tablet U was compared with either tablet N or R.

There were significant differences among average treatment areas 0–24 hr and among average peak plasma concentrations, but not among average areas 0–12 hr. Average time to reach peak plasma concentration demonstrated a significant difference when tablet U was compared with tablet D.

The coefficients of variation of the averages shown in Table IV are given in Table X.

### Relationship Between Prednisone and Prednisolone Plasma Levels in Study 2

Since prednisone is assumed to be biologically inactive, and prednisolone is assumed to be the biologically active steroid, the proportions of these two steroids in plasma are of interest. Tablet average plasma prednisone and prednisolone levels obtained in Study 2 are plotted in Fig. 1. Table V presents the average percentages

$$\frac{\text{concentration of prednisone}}{\text{concentration of prednisone} + \text{concentration of prednisolone}} \times 100$$

by tablet at each sampling time. Two observations can be made from these

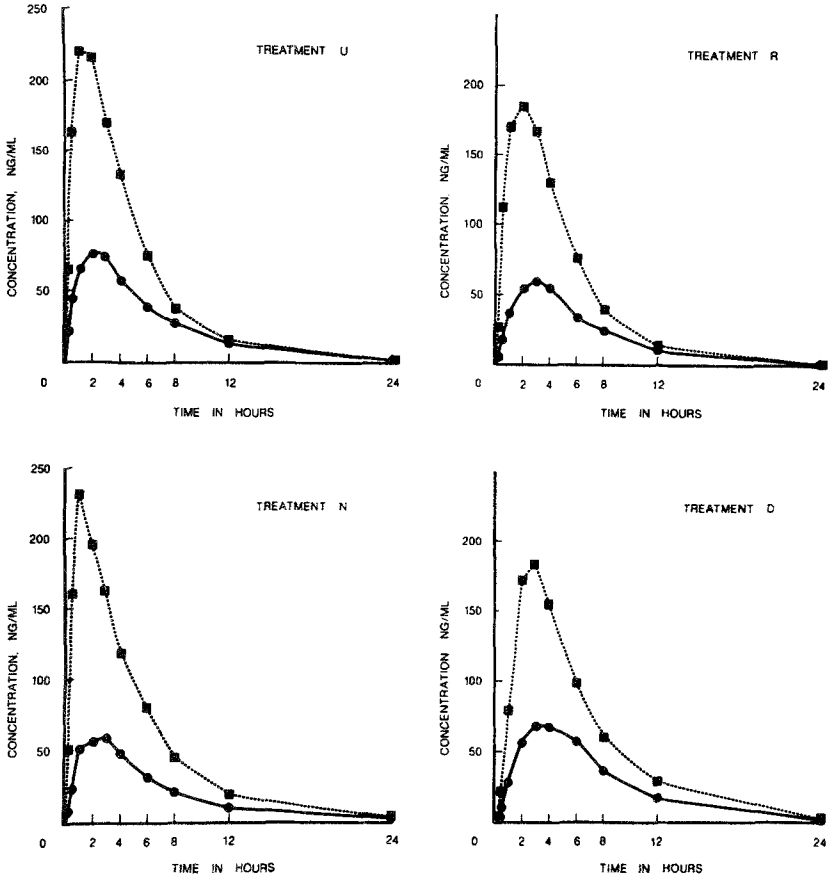


Fig. 1. Average plasma concentrations of prednisone (●) and prednisolone (■) from Study 2.

data. First, this percentage is not constant over the entire time course. The percentage generally increases with time and is highest at the tail end of the plasma level curve. An exception occurred with tablet U at the very early sampling times of 0.25 hr, when the percentage was high. The percentage is not, however, directly related to plasma prednisone levels.

Table VI shows that the above percentage depends on the tablet administered, particularly during the absorption–distribution phase (0.25–3 hr). When the "standard" tablet (U) was compared to tablets N, R, and D, there were differences between these average percentages at seven of the nine sampling times for tablet N, six of the nine sampling times for tablet R,

**Table V.** Percentages: 100 × Plasma Concentration of Prednisone/(Plasma Concentration of Predisone + Plasma Concentration of Prednisolone) with Time and Treatment for Study 2

| Tablet | Parameter | Percentage at indicated time in hr | | | | | | | | | Overall mean C.V. (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 0.25 | 0.5 | 1 | 2 | 3 | 4 | 6 | 8 | 12 | |
| U | Mean C.V. (%) | 28.8[a] | 21.8 | 23.2 | 26.8 | 31.0 | 31.0 | 35.4 | 44.9 | 49.1 | 32.5 |
| | | 25.2 | 14.3 | 12.1 | 13.6 | 15.2 | 15.2 | 18.5 | 23.5 | 19.7 | (33.3) |
| N | Mean C.V. (%) | 15.7 | 13.8 | 19.0 | 23.1 | 26.6 | 29.8 | 28.1 | 32.5 | 35.0 | 24.7 |
| | | 53.8 | 13.8 | 17.7 | 17.9 | 23.4 | 23.8 | 15.6 | 23.8 | 25.5 | (37.1) |
| R | Mean C.V. (%) | 13.5[b] | 13.8 | 17.2 | 22.6 | 26.6 | 30.3 | 31.5 | 40.1 | 41.7 | 27.0 |
| | | 46.2 | 35.7 | 17.6 | 17.8 | 20.3 | 12.2 | 20.2 | 23.2 | 23.3 | (42.6) |
| D | Mean C.V. (%) | —[c] | 35.7[d] | 30.4[e] | 26.6 | 27.9 | 30.9 | 33.5 | 39.0 | 37.9 | 33.0 |
| | | | 31.1 | 34.9 | 23.3 | 15.8 | 8.28 | 9.00 | 16.4 | 12.9 | (24.7) |

[a] $N = 11$ since subject 1 gave zero prednisone level.
[b] $N = 6$ since subjects 1, 3, 4, 5, and 10 gave zero prednisone or prednisolone level.
[c] Not calculated since 11 out of 12 subjects gave zero prednisolone level.
[d] $N = 10$ since subjects 4 and 10 gave zero prednisolone level.
[e] $N = 11$ since subject 10 gave zero prednisolone level.

**Table VI.** Results of Ordinary $t$ Tests ($t$) and Paired $t$ Tests ($t^*$) for Average Percentages Shown in Table V

| Time (hr) | Tablet U vs. Tablet N | Tablet U vs. Tablet R | Tablet U vs. Tablet D |
|---|---|---|---|
| 0.25 | $t = 3.95$<br>$p < 0.001$ | $t = 4.59$<br>$p < 0.001$ | — |
| 0.5 | $t^* = 7.71$<br>$p < 0.001$ | $t^* = 3.90$<br>$0.01 > p > 0.001$ | $t = 4.18$<br>$0.01 > p > 0.001$ |
| 1 | $t^* = 3.16$<br>$0.01 > p > 0.001$ | $t^* = 4.09$<br>$0.01 > p > 0.001$ | $t = 2.27$<br>$0.05 > p > 0.02$ |
| 2 | $t^* = 2.14$<br>N.S. ($p > 0.05$) | $t^* = 2.50$<br>$0.05 > p > 0.02$ | $t^* = 0.0765$<br>N.S. ($p > 0.25$) |
| 3 | $t^* = 2.45$<br>$0.05 > p > 0.02$ | $t^* = 2.21$<br>$0.05 > p > 0.02$ | $t^* = 1.73$<br>N.S. ($p > 0.10$) |
| 4 | $t^* = 0.47$<br>N.S. ($p > 0.25$) | $t^* = 0.41$<br>N.S. ($p > 0.25$) | $t^* = 0.021$<br>N.S. ($p > 0.25$) |
| 6 | $t^* = 2.73$<br>$0.05 > p > 0.01$ | $t^* = 2.10$<br>N.S. ($0.10 > p > 0.05$) | $t^* = 1.17$<br>N.S. ($p > 0.20$) |
| 8 | $t^* = 2.89$<br>$0.05 > p > 0.01$ | $t^* = 1.47$<br>N.S. ($p > 0.10$) | $t^* = 1.90$<br>N.S. ($0.10 > p > 0.05$) |
| 12 | $t = 3.63$<br>$0.005 > p > 0.001$ | $t^* = 2.43$<br>$0.05 > p > 0.01$ | $t^* = 4.78$<br>$p < 0.001$ |

and at four of the nine sampling times for tablet D, since the 0.25 hr must be included in the count for the last tablet for the reason explained in the footnote to Table V.

It is interesting that the average percentages taken over all sampling times and tablets are relatively constant from subject to subject (Table VII).

**Table VII.** Average Percentage[a] by Subject

| Subject | Mean | C.V. (%) |
|---|---|---|
| 1 | 28.6 | 32.7 |
| 2 | 27.3 | 34.0 |
| 3 | 26.4 | 35.2 |
| 4 | 33.4 | 33.9 |
| 5 | 27.5 | 34.4 |
| 6 | 27.1 | 33.2 |
| 7 | 27.9 | 41.5 |
| 8 | 29.1 | 51.2 |
| 9 | 32.7 | 38.3 |
| 10 | 29.6 | 27.7 |
| 11 | 28.6 | 30.8 |
| 12 | 32.4 | 31.6 |

[a]Percentage = 100 × plasma concentration of prednisone/(plasma concentration of prednisone + plasma concentration of prednisolone).

### Half-Lives of Prednisone and Prednisolone in Study 2

There were no significant differences among average treatment half-lives of either prednisone or prednisolone (Table III and IV). The overall average half-lives of prednisone and prednisolone were 3.59 and 2.93 hr, respectively. The half-lives measured in the individual subjects are shown in Table VIII according to treatment.

A paired $t$ test was used to show that the difference between average half-lives of prednisone and prednisolone was significant ($p < 0.001$). That is, the plasma half-lives of prednisone and prednisolone are different, with that of prednisone being longer than that of prednisolone.

### Plasma Levels of Prednisolone in Study 3

Tables IX and X summarize the results of the third prednisone study. In this study as in Study 1 (6) only prednisolone plasma concentrations were measured. ANOVA of plasma concentrations indicated highly significant tablet differences among average plasma concentrations of prednisolone at all sampling times through 2 hr. Tablet S was selected as the "standard" in this study, and when it was compared to the other tablets using Dunnett's multiple comparison procedure only the comparison of tablet S vs. tablet B gave consistently significant differences between average plasma concentrations through 2 hr. Similarly, the average peak plasma concentration following tablet S was significantly different from the average for tablet B.

Tablet L was significantly different from tablet S only when the average plasma concentration of prednisolone at 0.25 hr was compared. Tablet Mc was significantly different from tablet S when the average plasma concentrations of prednisolone at 2 hr and the average areas (0–12 hr) following these tablets were compared. No other difference among tablet averages was significant for the parameters tested.

The results of these two studies support the conclusion of a previous prednisone bioavailability study (6): that of the commercial prednisone tablets which have been studied in this laboratory (now numbering ten) these tablets differ mainly in the rate of appearance of prednisolone in the plasma but most probably not in the amount of prednisolone which reaches the circulation. That the results document that differences in *in vivo* rates of appearance of prednisolone in man correlate with *in vitro* rates of dissolution of prednisone will be demonstrated in a subsequent report.

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**Table VIII.** Half-Lives of Prednisone and Prednisolone (Study 2)

| | Half-life (hr) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Treatment N | | Treatment D | | Treatment U | | Treatment R | |
| Subject | Prednisone | Prednisolone | Prednisone | Prednisolone | Prednisone | Prednisolone | Prednisone | Prednisolone |
| 1 | 2.80 | 3.11 | 3.81 | 3.02 | 4.11 | 2.40 | 3.22 | 3.03 |
| 2 | 2.59 | 3.46 | 3.72 | 2.77 | 4.31 | 2.39 | 3.02 | 2.48 |
| 3 | 3.73 | 3.18 | 3.34 | 2.83 | 2.85 | 2.48 | 2.62 | 3.05 |
| 4 | 3.16 | 3.25 | 3.27 | 2.41 | 2.85 | 1.90 | 2.45 | 2.19 |
| 5 | 4.36 | 3.15 | 3.24 | 4.48 | 4.58 | 3.10 | 7.16 | 2.83 |
| 6 | 5.16 | 2.39 | 3.61 | 3.20 | 2.71 | 2.22 | 2.67 | 2.03 |
| 7 | 4.10 | 3.68 | 2.92 | 4.73 | 3.69 | 2.58 | 2.95 | 2.41 |
| 8 | 3.50 | 2.25 | 3.61 | 2.37 | 3.99 | 2.00 | 3.70 | 2.19 |
| 9 | 4.33 | 2.29 | 3.70 | 4.72 | 2.67 | 1.87 | 3.61 | 1.92 |
| 10 | 3.69 | 2.76 | 4.17 | 3.95 | 3.54 | 2.39 | 4.73 | 8.43 |
| 11 | 3.55 | 3.17 | 3.55 | 3.15 | 3.91 | 2.40 | 2.05 | 3.05 |
| 12 | 4.25 | 2.74 | 3.78 | 3.18 | 4.03 | 2.54 | 3.14 | 2.30 |
| Average | 3.77 | 2.95 | 3.56 | 3.40 | 3.60 | 2.36 | 3.44 | 2.99 |
| C.V. (%) | 19.2 | 15.7 | 9.24 | 25.1 | 18.7 | 14.4 | 39.5 | 58.8 |

**Table IX.** Summary of Results of Prednisone Study 3: Prednisolone Plasma Concentrations

| Parameter | Treatment averages | | | | Probability (among treatment averages) | Dunnett's multiple comparison test ($p \leq 0.05$) | | |
|---|---|---|---|---|---|---|---|---|
| | L | B | Mc | S | | S vs. L | S vs. B | S vs. Mc |
| Plasma concentration (ng/ml) at | | | | | | | | |
| 0.25 hr | 32.3 | 21.5 | 47.2 | 85.2 | $0.001 < p < 0.005$ | Sig.[a] | Sig. | N.S.[b] |
| 0.5 | 162 | 108 | 162 | 197 | $0.010 < p < 0.025$ | N.S. | Sig. | N.S. |
| 1 | 244 | 186 | 225 | 248 | $0.001 < p < 0.005$ | N.S. | Sig. | N.S. |
| 2 | 230 | 201 | 209 | 235 | $0.001 < p < 0.005$ | N.S. | Sig. | Sig. |
| 3 | 184 | 190 | 181 | 192 | N.S. ($p > 0.25$) | N.S. | N.S. | N.S. |
| 4 | 140 | 149 | 133 | 149 | N.S. ($0.10 < p < 0.25$) | N.S. | N.S. | N.S. |
| 6 | 75.2 | 87.1 | 77.3 | 79.2 | N.S. ($0.10 < p < 0.25$) | N.S. | N.S. | N.S. |
| 8 | 37.1 | 49.7 | 37.8 | 40.7 | $0.001 < p < 0.005$ | N.S. | Sig. | N.S. |
| 12 | 14.9 | 18.4 | 14.8 | 14.2 | N.S. ($0.10 < p < 0.025$) | N.S. | N.S. | N.S. |
| 24 | 3.01 | 1.84 | 2.37 | 2.67 | N.S. ($p > 0.25$) | N.S. | N.S. | N.S. |
| Area 0–24 hr [(ng/ml) × hr] | 1274 | 1280 | 1232 | 1342 | N.S. ($0.05 < p < 0.10$) | N.S. | N.S. | N.S. |
| Area 0–12 hr [(ng/ml) × hr] | 1167 | 1158 | 1129 | 1241 | $0.010 < p < 0.025$ | N.S. | N.S. | Sig. |
| Peak plasma concentration (ng/ml) | 252 | 213 | 259 | 266 | $p < 0.001$ | N.S. | Sig. | N.S. |
| Half-life (hr) | 2.49 | 2.67 | 2.44 | 2.36 | N.S. ($0.10 < p < 0.25$) | N.S. | N.S. | N.S. |
| Time to peak plasma level (min) | 85.2 | 118 | 79.8 | 77.4 | N.S. ($0.05 < p < 0.10$) | N.S. | N.S. | N.S. |

[a]Sig.: difference between treatment means is significant at $p \leq 0.05$.
[b]N.S.: difference between treatment means is not significant at the 5% level or less.

**Table X.** Coefficients of Variation of Averages Given in Tables III, IV, and IX

| | Coefficient of variation (%) | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Study 2 | | | | | | | | Study 3 | | | |
| | Prednisone | | | | Prednisolone | | | | Prednisolone | | | |
| Parameter | U | N | R | D | U | N | R | D | L | B | Mc | S |
| Plasma concentration (ng/ml) at | | | | | | | | | | | | |
| 0.25 hr | 61.8 | 88.2 | 124 | 190 | 92.2 | 87.0 | 147 | 346 | 72.5 | 76.5 | 98.9 | 94.5 |
| 0.5 | 36.5 | 32.8 | 68.7 | 63.5 | 41.2 | 42.1 | 72.8 | 89.2 | 36.9 | 59.1 | 62.6 | 44.0 |
| 1 | 16.3 | 25.7 | 38.3 | 42.4 | 15.3 | 18.9 | 35.5 | 77.8 | 11.1 | 21.2 | 31.0 | 20.2 |
| 2 | 13.2 | 23.2 | 23.3 | 26.8 | 17.4 | 18.7 | 13.7 | 43.2 | 11.1 | 12.5 | 17.2 | 10.1 |
| 3 | 17.2 | 22.6 | 18.9 | 25.5 | 17.5 | 20.6 | 17.5 | 32.5 | 14.8 | 12.0 | 17.4 | 15.6 |
| 4 | 15.1 | 25.5 | 15.9 | 24.8 | 25.9 | 26.4 | 21.8 | 30.4 | 17.7 | 16.1 | 22.6 | 17.5 |
| 6 | 19.3 | 27.7 | 25.6 | 18.0 | 30.0 | 28.1 | 36.5 | 26.9 | 27.9 | 25.1 | 25.1 | 13.6 |
| 8 | 20.4 | 39.5 | 27.8 | 21.7 | 46.2 | 38.4 | 34.4 | 29.7 | 38.3 | 27.1 | 29.4 | 22.5 |
| 12 | 35.7 | 30.4 | 65.5 | 20.2 | 46.3 | 53.3 | 48.4 | 28.2 | 39.3 | 25.9 | 34.6 | 32.4 |
| 24 | 179 | 138 | 214 | 153 | 346 | 181 | 346 | 198 | 125 | 178 | 188 | 165 |
| Area 0–24 hr [(ng/ml) × hr] | 14.3 | 20.4 | 19.2 | 14.4 | 19.6 | 19.8 | 14.6 | 21.7 | 13.5 | 13.1 | 12.9 | 7.5 |
| Area 0–12 hr [(ng/ml) × hr] | 14.3 | 21.9 | 13.8 | 16.1 | 18.1 | 20.3 | 13.6 | 23.7 | 12.3 | 12.7 | 12.3 | 7.46 |
| Peak plasma concentration (ng/ml) | 13.9 | 23.5 | 14.0 | 23.2 | 15.5 | 17.4 | 12.5 | 29.2 | 8.25 | 11.0 | 13.1 | 12.3 |
| Time to peak plasma level (min) | 31.9 | 43.2 | 35.1 | 29.2 | 46.7 | 46.0 | 49.7 | 25.9 | 47.2 | 46.8 | 56.2 | 60.6 |

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