

## Bioavailability of Prednisolone Tablets

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*Two four-treatment crossover studies were performed using 12 adult male volunteers in each with seven different commercially available prednisolone tablets. Plasma samples were assayed for prednisolone by a radioimmunoassay method. Statistical analyses of the data, by analysis of variance for crossover design (ANOVA), showed no significant differences among the treatment averages at any of the sampling times except at 0.25 and 4 hr in one of the studies. There were also no significant differences among the treatment averages for peak plasma level, time of peak plasma level, area 0–12 hr, area 0–24 hr, and the half-life of elimination of prednisolone. We conclude that the average plasma concentrations of prednisolone are superimposable in a statistical sense and that the tablets tested are bioequivalent. Results of dissolution studies of six tablets of each of the seven lots of prednisolone tablets, using deaerated water in the spin filter apparatus, are presented.*

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**KEY WORDS:** prednisolone bioavailability; prednisolone radioimmunoassay; prednisolone plasma concentrations; elimination half-life of prednisolone; *in vitro* rate of dissolution of prednisolone from tablets.

### INTRODUCTION

Prednisolone, 11 $\beta$ ,17,21-trihydroxypregna-1,4-dien-3,20-dione, is a potent corticosteroid that is offered for the palliative treatment of rheumatoid arthritis and various other diseases. Partly because of the low solubility of the drug (1), the Ad Hoc Committee on Drug Product Selection

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of the Academy of General Practice of Pharmacy included prednisolone in a list of drugs susceptible to bioavailability problems (2). Since then very few studies have appeared in the literature reporting the biological availability of prednisolone; most of these were recently reviewed in a monograph on prednisolone (3). The reviewers noted that with the exception of one study (4) all studies suffer from a number of serious experimental defects. The investigators, in these reports either have used high doses of prednisolone and failed to follow plasma levels of the drug for more than two half-lives with an insensitive colorimetric assay method (5), or have used a nonspecific assay and also failed to use the recommended crossover experimental design (6), or have studied sustained release of enteric-coated preparations (7-10). In view of the limited information on the *in vivo* availability of the corticosteroid following the administration of single, low doses of prednisolone in the form of compressed tablets, the studies to be reported were done. This article reports the results of two four-treatment crossover studies utilizing seven different, commercially available tablets of prednisolone.

## EXPERIMENTAL

### Test Products

The prednisolone tablets studied were obtained from the open market by the Food and Drug Administration, who reported to the authors that the tablets had the following average percentage of declared potency (SD in parentheses): Mc, 98.6 (3.12); St, 103.2 (2.33); Re, 98.3 (2.51); U, 98.9 (1.21); R, 105.7 (3.91); ST, 99.0 (3.00); O, 94.3 (2.50). The code letter(s) are the first one or two letters of the names of the manufacturers, and lot numbers are given in the footnote to Table I.

### *In Vitro* Studies

The spin filter apparatus of Shah *et al.* (12) was used to perform *in vitro* dissolution rate studies. All the studies were performed at 37°C, using 1 liter of deaerated water as the dissolution medium. The dissolution studies on the same tablets are being repeated in 0.1 N hydrochloric acid using gold-plated equipment, but these results will be reported in a separate communication. The stirrer speed was maintained at 400 rpm for a period of 30 min and then it was changed to 800 rpm until a constant absorbance reading was attained. The constant absorbance value could be interpreted as the percentage of label dissolved in infinite time. Since ultraviolet-absorbing material in the tablet, other than prednisolone, may contribute to the percentage of labeled amount of prednisolone dissolved and/or the prednisolone in the

tablet may not all be released in a water system, the data are presented as "mean percentage of infinity dissolved," which is defined as the "mean percentage of label dissolved to an arbitrary time  $t$  divided by the mean percentage of label dissolved in infinite time."

### Subjects

In each study, 12 adult male volunteers with no known disease, who weighed between 54 and 95 kg and were between 21 and 33 years of age were selected. Six of the 12 subjects were common to both studies. The subjects had good venous systems in their arms to facilitate blood sampling. Before each subject could be included in the study, a complete physical and routine blood analysis and urinalysis were carried out. As a screening procedure, values for the following tests were required to be in the normal range: chloride, CO<sub>2</sub>, potassium, sodium, BUN, glucose, total protein, albumin, calcium phosphorus, cholesterol, uric acid, creatinine, total bilirubin, alkaline phosphatase, LDH<sub>2</sub>, SGOT, white cell count, hematocrit, hemoglobin, red cell count, and plasma 17-OHCS. Informed consent was obtained from all subjects.

A recent drug history was taken for each prospective subject. All subjects participating in the studies received no barbiturates or other enzyme-inducing agents for a period of 30 days preceding initiation of the studies, and none concurrent with them. They received no other medication or alcoholic beverages for a period of 7 days before initiation of the studies, and none during the study periods. After screening and acceptance for the studies, the subjects were assigned numbers and their body weight, age, height, race, and body build were recorded.<sup>4</sup>

### Treatment Schedule and Doses

The subjects started fasting at 10 P.M. the night before administration of prednisolone. At 11 P.M. that night, each subject took orally 1.0 mg dexamethasone (as two tablets of Decadron, 0.5 mg) to suppress endogenous cortisol secretion. Suppression of endogenous cortisol was necessary because cortisol cross-reacts with the prednisolone antiserum used in the radioimmunoassay. Dexamethasone does not cross-react with the prednisolone antiserum.

Within 1 hr after arising, on the first day of the studies, each subject drank 240 ml of water. At time zero, the subjects ingested 10 mg of prednisolone with 180 ml of water. The tablets were swallowed whole and not fractured or chewed before being swallowed. No food or beverages were

<sup>4</sup>The vital statistics of the subjects and all plasma concentrations measured in the two studies have been forwarded to the editor of this Journal to be placed in a repository.

Table I. Treatment Schedule

Study	Subjects	Group	Time periods			
			Week I	Week II	Week III	Week IV
2	1, 2, 3	1	Mc <sup>a</sup>	St	U	Re
	4, 5, 6	2	St <sup>b</sup>	Re	Mc	U
	7, 8, 9	3	Re <sup>c</sup>	U	St	Mc
	10, 11, 12	4	U <sup>d</sup>	Mc	Re	St
3	1, 2, 3	1	R <sup>e</sup>	SF	O	U
	4, 5, 6	2	ST <sup>f</sup>	U	R	O
	7, 8, 9	3	U <sup>d</sup>	O	ST	R
	10, 11, 12	4	O <sup>g</sup>	R	U	ST

<sup>a</sup>Mc = C.T. prednisolone, 5 mg (McKesson, lot 3J215).

<sup>b</sup>St = C.T. prednisolone, 5 mg (Stanley, lot 108-303).

<sup>c</sup>Re = C.T. prednisolone, 5 mg (Rexall, lot C41913).

<sup>d</sup>U = Delta-Cortef, 5 mg (Upjohn, lot 945CB).

<sup>e</sup>R = C.T. prednisolone, 5 mg (Rondex, lot 37111).

<sup>f</sup>ST = C.T. prednisolone, 2.5 mg (Stanley, lot 63402).

<sup>g</sup>O = C.T. prednisolone, 5 mg (Ormont, lot 151-6020).

permitted until 4 hr after dosing with prednisolone. From 4 hr after dosing with prednisolone, food and beverages were allowed *ad libitum*. Eight hours after the administration of prednisolone, the subjects were given another 0.5 mg tablet of dexamethasone to continue the suppression of hydrocortisone. A washout period of 1 week was allowed between treatments, a period of 2 months separated the two studies. The treatment schedules that were used in the two studies are shown in Table I.

### Blood Sampling

Fifty milliliters of blood was taken from the forearm vein just prior to dosing with prednisolone (time zero). A dilution of the 0-hr plasma was used in the construction of the calibration plot for the prednisolone radioimmunoassay. Subsequently, 10 ml of whole blood was drawn at 0.25, 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 hr after dosing with prednisolone. Each blood sample was centrifuged shortly after collection; the plasma was quick-frozen and kept in the frozen state ( $-20^{\circ}\text{C}$ ) until just prior to assay.

### Assay Method

Plasma samples obtained in Prednisolone Study No. 2<sup>5</sup> were analyzed by using the following procedure, using antiserum supplied by Dr. J. C. K.

<sup>5</sup>Prednisolone Study No. 1 was that reported by Sullivan *et al.* (4).

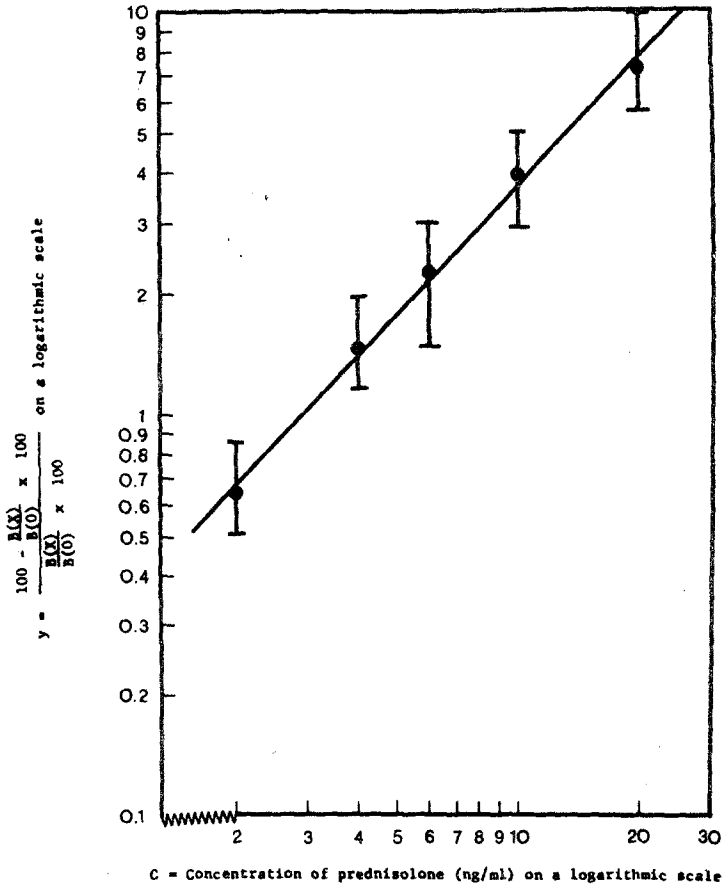
Loo. The samples were diluted so that 1 ml of the diluted plasma contained between 0.4 and 10 ng of drug. Usually unknown plasma samples were diluted 1:50 (same as in preparation of standard curve), but on reassay some had to be diluted 1:10 to get the concentration in range of the standard curve. One milliliter of diluted 0-hr plasma was spiked with 0, 0.4, 0.8, 2, 4, 6, and 10 ng of cold prednisolone for the binding curve. One milliliter of the diluted spiked plasma was extracted with 7 ml of dichloromethane for 5 min on a mechanical shaker. The sample was centrifuged and the aqueous phase was aspirated. A 5-ml aliquot of the organic phase was transferred to a disposable culture tube and evaporated to dryness under a stream of nitrogen. To the dried tube was added 50  $\mu$ l of absolute ethanol (wash sides), followed by 10  $\mu$ l of [ $^3$ H]prednisolone. One milliliter of saline phosphate buffer was then added (wash sides) followed by 10  $\mu$ l of a solution of the antiserum of Loo. The mixture was vortexed and incubated in a 37°C water bath for 15 min. At the end of the incubation time, the sample was placed in an ice bath and 0.5 ml of cold dextran-coated charcoal (5% charcoal, 0.5% dextran T<sub>70</sub>) was added. The sample was allowed contact with the charcoal suspension for exactly 10 min and then was centrifuged at 0°C and 2000 rpm for 15 min. The supernatant was quickly decanted into a scintillation vial containing 10 ml of Unogel and counted for 10 min.

The method of Sullivan *et al.* (4) was used to assay all samples obtained in Prednisolone Study No. 3, using antiserum of W. A. Colburn. Plasma samples were diluted to an appropriate degree so that 1 ml of diluted plasma contained 2–20 ng of drug. Usually unknown plasma samples were diluted 1:25 (same as in preparation of the standard curve), but on reassay some had to be diluted 1:10 to get the concentration in the range of the standard curve. The standard curve was constructed from diluted (1:25) 0-hr plasma that was spiked with 0, 2, 4, 6, 10, and 20 ng of unlabeled prednisolone.

All plasma concentrations of prednisolone were obtained by inverse estimation using the parameters of the least-squares line drawn through a logistic-logarithmic plot as indicated in

$$\ln y = \ln \left[ 100 - \frac{B(X)}{B(0)} \times 100 \right] / \left[ \frac{B(X)}{B(0)} \times 100 \right] = S \times \ln C + \ln Q \quad (1)$$

where  $B(0)$  represents the percent-bound value when there was no prednisolone added to plasma,  $B(X)$  represents the percent bound in the presence of prednisolone,  $S$  is the slope of the line,  $C$  is the concentration of prednisolone (ng/ml), and  $\ln Q$  is the intercept of the regression line fitted to the data. Figure 1 represents the calibration curve for Prednisolone Study No. 2. The authors have evidence which clearly shows that this method of estimating prednisolone levels is superior to the method of Sullivan *et al.* (4)



**Fig. 1.** Calibration data for prednisolone radioimmunoassay obtained by spiking diluted 0-hr plasma of the 12 subjects in Prednisolone Study No. 2. Circles represent  $e^{\overline{\ln y}}$  values, where  $\overline{\ln y}$  represents the average natural logarithms of the function shown on the ordinate scale for the 12 subjects. The bars mark off the range of values for the 12 subjects. The regression line has the equation  $\overline{\ln y} = 0.8853 \ln C + 0.4209$  and is based on 72 points. (See text for meaning of  $y$ .)

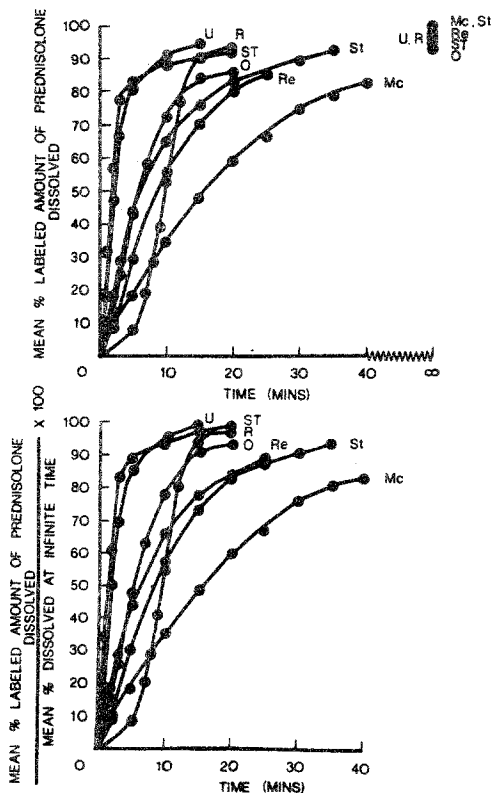
because it provides less bias in the calculated prednisolone concentrations. The authors would like to caution other investigators who work with radioimmunoassays that just because a logistic-logarithmic calibration plot works best for estimating plasma prednisolone levels, no inference is intended as to the superiority of this plot over other methods of calculating plasma levels of other compounds. For instance, the authors have evidence which indicates that a logistic-logarithmic plot is quite inadequate for

estimating plasma levels of either prednisone or digoxin. A detailed analysis of radioimmunoassay data for prednisolone, prednisone, and digoxin is given by two of the authors elsewhere (11).

## RESULTS AND DISCUSSION

### *In Vitro* Studies

Figure 2 shows the *in vitro* dissolution data obtained in the spin filter apparatus (12) for the seven tablets tested *in vivo*. Each point on each curve represents an average of six separate tablet determinations. There were marked differences in the *in vitro* rates of dissolution among the tablets. It is



**Fig. 2.** Dissolution data for the seven different tablets used in Prednisolone Studies No. 2 and 3 in the spin filter apparatus of Shah *et al.* (12). See footnotes to Table I for key to different tablets.

interesting to note that the 2.5 mg and 5.0 mg tablets (ST and St, respectively) of the same manufacturer released the drug at markedly different rates. The 2.5 mg tablet dissolved more rapidly and displayed a hyperbolic type of release curve, while the 5.0 mg tablet dissolved more slowly and displayed a sigmoid type of curve. All tablets were found to be equivalent with respect to availability in normal humans; therefore, for the tablets tested, absorption of prednisolone does not appear to be dissolution-rate controlled. All tablets apparently released prednisolone at an *in vivo* rate that was rapid enough so that this release did not rate-limit absorption in man.

### Assay Error

In Prednisolone Study No. 2 antiserum of J. C. K. Loo was utilized and the standard curve (Fig. 1) is based on 72 points (the 12 subjects' 0-hr plasma spiked at 0.4, 0.8, 2, 4, 6, and 10 ng prednisolone per milliliter of plasma).

The regression equation was

$$\widehat{\ln y} = 0.8853 \ln C + 0.4209 \quad (2)$$

The concentrations of prednisolone in "unknown" plasmas were estimated by means of the rearranged form of equation 2, namely,

$$\hat{C} = e^{(\ln y - 0.4209)/0.8853} \quad (3)$$

where  $\ln y$  is given by the middle portion of equation 1.

The coefficients of variation calculated from the inversely estimated concentrations ( $\hat{C}$ ), using the 12  $\ln y$  values at each concentration, were 17.9%, 11.8%, 13.1%, 14.6%, 14.0%, and 20.3% for the known standard concentrations ( $C_s$ ) of 0.4, 0.8, 2, 4, 6, and 10 ng/ml, respectively. So-called bias values may be calculated from the mean estimated concentrations ( $\hat{C}_m$ ) using

$$\text{bias value} = \left[ \frac{\hat{C}_m - C_s}{C_s} \right] \times 100 \quad (4)$$

The observed bias values were 1.3%, -3.6%, 6.5%, 7.3%, 0.3%, and -2.1%, respectively, for the concentrations in the same order.

In Prednisolone Study No. 3, antiserum of W. A. Colburn was utilized and a similar standard curve to that shown in Fig. 1 was obtained. The standard curve for this study was based on spiking the 0-hr plasmas of subjects 1-6 at 2, 4, 6, 10, and 20 ng prednisolone/ml plasma. Thus the standard curve was based on 30 points. This was done since in Prednisolone Study No. 2 the logistic-logarithmic equation based on the data from subjects 1-6 was essentially identical to that based on subjects 1-12.



Because the antiserum of W. A. Colburn was less sensitive than that of J. C. K. Loo, the logistic-logarithmic equation was different and is shown as

$$\widehat{\ln y} = 1.0593 \ln C - 1.1214 \quad (5)$$

The coefficients of variation estimated from the inversely estimated concentrations (as above) were 20.5%, 21.0%, 19.8%, 22.9%, and 26.3% for actual concentrations of 2, 4, 6, 10, and 20 ng/ml, respectively, and the bias values, calculated from the means, were -2.0%, 4.3%, 8.2%, 7.0%, and 3.5%, respectively, for concentrations in the same order.

The calibration data for each subject in each study were collected on a different day; hence the above figures include both intra- and inter-day variation.

### Plasma Levels of Prednisolone

The cross-reactivity of prednisolone, the prednisolone metabolite  $20\beta$ -dihydroprednisolone, and cortisol with the antiserum of W. A. Colburn has been previously reported (13). We demonstrated that plasma concentrations of prednisolone were identical when assayed by the two antisera. Hydrocortisone cross-reacts with both antisera. Hence, in order to obtain a

**Table II.** Summary of Results of Prednisolone Study No. 2

Parameter	Treatment averages				Results of ANOVA test for among-treatment averages
	U	Re	St	Mc	
Prednisolone plasma concentration (ng/ml)					
0.25 hr	71.7	46.3	50.8	31.2	NS ( $0.05 < p < 0.10$ )
0.50 hr	157.	146.	135.	136.	NS ( $p > 0.25$ )
1.0 hr	240.	228.	217.	211.	NS ( $p > 0.25$ )
2.0 hr	205.	206.	209.	200.	NS ( $p > 0.25$ )
3.0 hr	179.	167.	174.	163.	NS ( $p > 0.25$ )
4.0 hr	153.	128.	143.	144.	NS ( $0.10 < p < 0.25$ )
6.0 hr	90.6	90.6	87.8	89.5	NS ( $p > 0.25$ )
8.0 hr	53.2	45.4	50.7	49.1	NS ( $p > 0.25$ )
12.0 hr	17.3	15.6	17.8	17.1	NS ( $p > 0.25$ )
24.0 hr	2.35	1.68	3.26	2.00	NS ( $0.1 < p < 0.25$ )
Peak plasma level (ng/ml)	257.	238.	238.	232.	NS ( $p > 0.25$ )
Time of peak plasma level (hr)					
	1.42	1.25	1.13	1.50	NS ( $p > 0.25$ )
Area 0-12 hr [(ng/ml) × hr]					
	1246.	1129.	1187.	1157.	NS $0.10 < p < 0.25$ )
Area 0-24 hr [(ng/ml) × hr]					
	1364.	1233.	1314.	1271.	NS ( $0.10 < p < 0.25$ )
Half-life (hr)					
	2.55	2.60	2.77	2.62	NS ( $p > 0.25$ )

more specific assay for prednisolone, it was necessary to suppress adrenal function with dexamethasone.

The average plasma concentrations of prednisolone following the four different treatments studied in Prednisolone Study No. 2 are summarized in Table II. There were no significant differences among the treatment average plasma concentrations at any sampling time. There were no significant differences among the treatment averages for peak plasma concentration, area 0–12 hr, area 0–24 hr, or the apparent half-life of elimination of prednisolone. The coefficients of variation of the averages shown in Table II are given in Table III.

The average plasma concentrations of prednisolone following the oral administration of the four treatments studied in Prednisolone Study No. 3 are summarized in Table IV. There were statistically significant differences among the treatment average plasma concentrations at 0.25 and 4 hr, but not at all other sampling times. There were also no significant differences among the treatment averages for peak plasma concentration, area 0–12 hr, area 0–24 hr, or the apparent half-life of prednisolone. Table V gives the coefficients of variation of the averages shown in Table IV.

Another important consideration is the power of the analysis of variance. If the hypothesis that the means were equal was false, a so-called type

**Table III.** Coefficients of Variation of Treatment Averages Given in Table II

Parameter	Coefficients of variation (%) for treatments				C.V.(%) from RMS <sup>a</sup> of ANOVA <sup>b</sup>
	U	Re	St	Mc	
Plasma concentration (ng/ml)					
0.25 hr	74.9	80.7	83.3	86.1	67.9
0.50 hr	42.1	37.9	40.3	50.1	42.5
1.0 hr	18.9	17.4	19.9	32.6	21.2
2.0 hr	11.0	15.0	18.2	26.7	15.1
3.0 hr	12.3	12.9	16.5	25.0	14.4
4.0 hr	29.1	12.7	19.5	22.4	18.8
6.0 hr	23.3	14.6	18.7	23.8	18.6
8.0 hr	33.9	16.4	21.1	27.4	26.5
12.0 hr	41.6	42.9	33.1	45.7	35.9
24.0 hr	91.0	124.	87.2	110.	84.5
Peak plasma level (ng/ml)	10.1	14.1	12.0	22.4	13.9
Time of peak plasma level (hr)	70.3	57.8	38.5	60.3	72.7
Area 0–12 hr [(ng/ml) × hr]	10.8	8.58	10.8	19.0	10.7
Area 0–24 hr [(ng/ml) × hr]	13.0	9.5	12.1	19.0	11.9
Half-life (hr)	22.6	14.6	18.4	15.5	13.2

<sup>a</sup>RMS = residual mean square.

<sup>b</sup>ANOVA = analysis of variance for crossover design.

Table IV. Summary of Results of Prednisolone Study No. 3

Parameter	Treatment averages				Results of ANOVA test for among-treatment averages
	R	ST	O	U	
Prednisolone plasma concentration (ng/ml)					
0.25 hr	22.1	86.9	36.9	47.2	$0.025 < p < 0.05$
0.50 hr	106.	180.	167.	165.0	NS ( $0.05 < p < 0.1$ )
1.0 hr	223.	255.	257.	234.0	NS ( $p > 0.25$ )
2.0 hr	212.	232.	228.	238.0	NS ( $p > 0.25$ )
3.0 hr	178.	199.	182.	202.0	NS ( $p > 0.25$ )
4.0 hr	125.	158.	138.	154.0	$0.025 < p < 0.05$
6.0 hr	71.1	92.2	76.4	83.7	NS ( $0.05 < p < 0.1$ )
8.0 hr	37.0	45.7	36.5	43.4	NS ( $p > 0.25$ )
12.0 hr	10.4	18.2	13.1	12.6	NS ( $0.1 < p < 0.25$ )
24.0 hr	1.62	4.34	4.45	3.30	NS ( $p > 0.25$ )
Peak plasma level (ng/ml)	240.0	262.0	263.0	254.0	NS ( $p > 0.25$ )
Time of peak plasma level (hr)	1.42	1.21	1.00	1.33	NS ( $p > 0.25$ )
Area 0-12 hr [(ng/ml) × hr]	1052.	1307.	1171.	1242.	NS ( $0.05 < p < 0.1$ )
Area 0-24 hr [(ng/ml) × hr]	1124.	1442.	1276.	1337.	NS ( $0.05 < p < 0.1$ )
Half-life (hr)	2.12	2.44	2.30	2.26	NS ( $p > 0.25$ )

II error ( $\beta$  error) would occur if the tested hypothesis was accepted when it was false. The probability of rejecting the tested hypothesis when it was false is called "the power of the test against a specified alternative" and is denoted as  $1 - \beta$ . For example, if  $1 - \beta = 0.8$ , then the chances are 0.8 out of 1.0 of detecting the specified difference in means. Table VI lists values of  $1 - \beta$  which were calculated, using the coefficients of variation in the last columns of Tables III and V, by the method of Dixon and Massey (14) as illustrated for crossover studies by Wagner (15). Calculations were made for both a 20% and a 30% difference in extreme means with  $\alpha = 0.05$ . As is usual in such evaluations of most bioavailability data, the  $1 - \beta$  values vary widely—in this case, from  $< 0.3$  to  $> 0.99$ . The  $1 - \beta$  values are  $\geq 0.8$ , the usually desired values, for plasma concentrations at 1, 2, 3, 4, and 6 hr, peak plasma level, area 0-12 hr, area 0-24 hr, and half-life when the specified difference in extreme means is 30%; nine of the values are  $\geq 0.8$  when the specified difference in extreme means is 20%. Our conclusion of bioequivalence (below) is principally based on the results of analyses of variance of the areas and the peak concentrations, and for these parameters there is excellent power usually with the 20% difference and always with the 30% difference. Although some readers may disagree with inclusion of Fig. 3 (discussed

Table V. Coefficients of Variation of Treatment Averages Given in Table IV

Parameter	Coefficients of variation (%) for treatments				C.V.(%) from RMS <sup>a</sup> of ANOVA <sup>b</sup>
	R	ST	O	U	
Plasma concentration (ng/ml)					
0.25 hr	80.2	97.1	86.1	116.	114.
0.5 hr	43.2	51.4	47.1	48.3	45.6
1.0 hr	28.7	22.9	18.9	17.2	21.2
2.0 hr	20.1	18.0	15.4	16.2	15.0
3.0 hr	26.8	20.2	21.0	20.5	18.3
4.0 hr	28.1	23.6	19.0	19.1	19.6
6.0 hr	43.7	33.8	22.0	26.7	25.9
8.0 hr	65.6	52.2	35.4	40.9	38.0
12.0 hr	66.7	73.7	44.2	40.9	57.6
24.0 hr	142.	74.8	104.	153.	124.
Peak plasma level (ng/ml)	20.1	20.1	16.2	12.2	15.2
Time of peak plasma level (hr)	47.2	47.2	36.9	46.2	43.9
Area 0-12 hr [(ng/ml)×hr]	26.5	26.8	18.4	17.6	19.0
Area 0-24 hr [(ng/ml)×hr]	28.4	30.2	20.5	19.0	29.0
Half-life (hr)	14.0	25.3	14.5	13.0	17.8

<sup>a</sup>RMS = residual mean square.<sup>b</sup>ANOVA = analysis of variance for crossover design.

Table VI. Values of the Power (1-β) of the Analyses of Variance Using Coefficients of Variation in the Last Columns of Tables III and V and Extreme Means Differing by Both 20% and 30%

Parameter	1-β			
	Prednisolone Study No. 2		Prednisolone Study No. 3	
	20% <sup>a</sup>	30% <sup>b</sup>	20% <sup>a</sup>	30% <sup>b</sup>
Plasma concentration (ng/ml)				
0.25 hr	<0.3	<0.3	<0.3	<0.3
0.50 hr	<0.3	0.35	<0.3	<0.3
1.0 hr	0.50	0.94	0.50	0.92
2.0 hr	0.86	>0.99	0.86	>0.99
3.0 hr	0.89	0.99	0.65	0.985
4.0 hr	0.65	0.98	0.62	0.965
6.0 hr	0.65	0.98	0.38	0.80
8.0 hr	0.38	0.78	<0.3	0.43
12.0 hr	<0.3	0.50	<0.3	<0.3
24.0 hr	<0.3	<0.3	<0.3	<0.3
Peak plasma level (ng/ml)	0.91	>0.99	0.86	>0.99
Time of peak plasma level (hr)	<0.3	<0.3	<0.3	0.33
Area 0-12 hr [(ng/ml)×hr]	>0.99	>0.99	0.65	0.978
Area 0-24 hr [(ng/ml)×hr]	0.978	>0.99	0.50	0.942
Half-life (hr)	0.94	>0.99	0.72	0.986

<sup>a</sup>Calculated for extreme means differing by 20% and specifically for means of 100, 93.3, 86.7, and 80.<sup>b</sup>Calculated for extreme means differing by 30% and specifically for means of 100, 90, 80, and 70 using the method of Dixon and Massey (14).

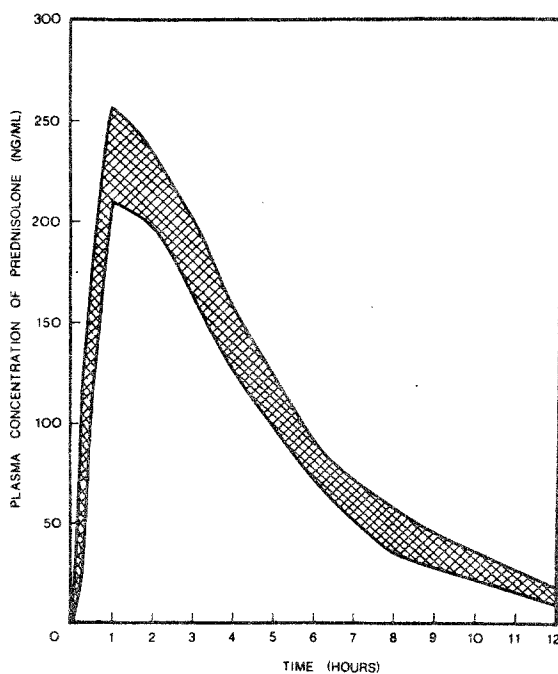


Fig. 3. Hatched area, bounded by the two solid lines, includes the average prednisolone plasma concentrations following oral administration of 10 ng of prednisolone as nine different prednisolone tablets made by eight different manufacturers which were studied in Prednisolone Studies No. 1, 2, and 3.

below), since it is a cross-study comparison involving different subjects, the authors wished to include it for clinically oriented readers, who, the authors believe, would also conclude bioequivalency.

Figure 3 summarizes the average prednisolone concentrations in all three prednisolone studies, where Prednisolone Study No. 1 was previously reported by Sullivan *et al.* (4). The plot includes data obtained with prednisolone tablets from nine different tablets made by eight different manufacturers. In light of the statistics reported for each of the three studies, the authors conclude that the average prednisolone concentrations are superimposable and that the nine different tablets tested are bioequivalent. The authors would like to caution that this conclusion not be extrapolated to all marketed prednisolone tablets.

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