Bioavailability of Hydrocortisone From Commercial 20-mg Tablets

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Abstract □ The relative bioavailability of hydrocortisone was determined from four different 20-mg tablet formulations and one suspension in 15 healthy male volunteers; results were compared with *in vitro* dissolution rates. Plasma levels of hydrocortisone were determined by a liquid chromatography method developed in this laboratory. Dissolution of the tablet formulations, using the official USP test, varied from 7.8 to 93.8% in 30 min. Similar plasma profiles were obtained from all tablet products, and there were no differences among tablets in the cumulative percentage of drug absorbed. There were no clear trends in any pharmacokinetic parameter values among the tablet dosages, and the four products were considered bioequivalent. The suspension dosage yielded significantly higher plasma levels compared with some of the tablet formulations during the initial 30-min postdose, significantly higher cumulative absorption at 0.5 and 1.0 h compared with one tablet formulation, and significantly higher k_a and C_{max}, and shorter t_{max} values, compared with some of the tablets.

Keyphrases □ Hydrocortisone—bioavailability, commercial 20-mg tablets, dissolution □ Bioavailability—hydrocortisone, commercial 20-mg tablets, dissolution □ Dissolution—bioavailability of hydrocortisone, commercial 20-mg tablets

Hydrocortisone was designated by the U.S. Food and Drug Administration as a drug whose different brands and dosage forms should be examined for bioequivalence (1). Previous studies in this laboratory have described optimum conditions for hydrocortisone pharmacokinetic studies (2, 3). Circulating hydrocortisone levels have been shown to be linearly related to dose size of oral suspensions (4) and also of intravenous hydrocortisone doses that give rise to plasma levels that are within the range observed with conventional oral doses (5).

This study was designed to examine the relative *in vivo* bioavailability and pharmacokinetics of hydrocortisone from commercial 20-mg tablets that have divergent *in vitro* dissolution characteristics, and to compare these with an oral suspension.

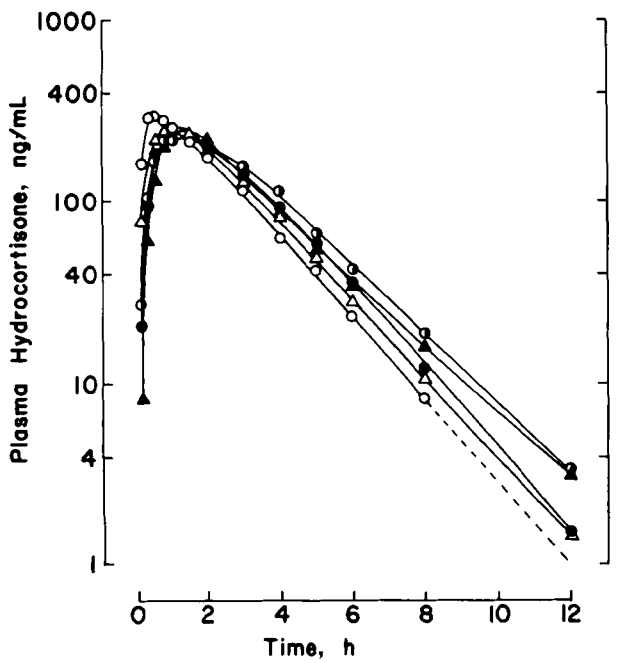

Figure 1— *Mean plasma levels of hydrocortisone in 15 healthy male volunteers following single 20-mg suspension and tablet doses. Key: (○) suspension A; (◑) tablet B; (●) tablet C; (△) tablet D; (▲) tablet E.*

EXPERIMENTAL SECTION

Products—The suspension[1] (treatment A) and the four tablet[2] formulations (treatments B–E) were purchased commercially.

Materials—Chemical standard hydrocortisone[3] and internal standard Δ^4-pregnen-17α,20β,21-triol-3,11-dione[3] were analytical grade. All other solvents and chemicals were reagent grade and were used as supplied. Plasma for construction of standard curves was obtained from healthy volunteers between 7 a.m. and 9 a.m. subsequent to administration of 2 mg of dexamethasone at 11 p.m. the previous day.

***In Vitro* Dissolution**—The *in vitro* dissolution rates of the tablets were determined in 900 mL of distilled water at 37°C using the USP rotating paddle method at 50 rpm (6).

Subjects—Fifteen male volunteers, 22–39 years old, underwent complete physical examinations, including urine and blood analyses, after giving informed consent. Vital signs and laboratory values for all subjects were normal. The subjects weighed 67–84 kg, and their heights ranged from 165 to 186 cm.

Protocol—Subjects were instructed to take no drugs for at least 1 week before, and no drugs other than the required doses of dexamethasone and hydrocortisone during the study. No caffeine-containing beverages were permitted for 1 d before or during the plasma sampling period following each dose of hydrocortisone. Each hydrocortisone dose was administered after an overnight fast, and no food was permitted until 4 h postdose.

The 15 subjects were randomly assigned to one of five groups, each consisting of three subjects. The five dosages (one suspension and four tablets) were administered to the groups according to a 5 × 5 crossover design. Dose size was 20 mg, and all dosages were separated by a 14-d interval.

At 11 p.m. on the day before hydrocortisone administration, subjects received 20 mL (2 mg) of dexamethasone elixir[4] orally together with 180 mL of water. Dexamethasone suppresses plasma levels of endogenous hydrocortisone (2). Hydrocortisone was administered the next morning at 8 a.m. The suspension was given in 20 mL of orange juice with additional water to 180 mL. Tablets were given with 180 mL of water and were swallowed whole. Heparinized blood samples (~8 mL) were taken from a forearm vein at 0, 10, 20, 30, 45 min, 1, 1.5, 2, 3, 4, 5, 6, 8, and 12 h postdose. Plasma was stored at −20°C until assayed.

Analytical Procedure—The HPLC-UV assay used to measure hydrocortisone in plasma was described previously (3, 4). The assay is linearly sensitive to plasma hydrocortisone concentrations between 5 and 700 ng/mL. The reproducibility of the assay is within 4% at the higher concentrations and within 8% at the lower concentrations. Suppressed hydrocortisone concentrations obtained immediately prior to drug administration were subtracted from all measured postdose levels.

[1] (A) Cortef intramuscular suspension, 50 mg/mL, Lot No. 027FP; The Upjohn Co.

[2] (B) Cortef, 20 mg, Lot No. 446GT; The Upjohn Co. (C) Hydrocortisone, 20 mg, Lot No. 9C483; McKesson Laboratories. (D) Hydrocortone, 20 mg, Lot No. D1048; Merck Sharp and Dohme. (E) Hydrocortisone, 20 mg, Lot No. 33993; Richlyn.

[3] Sigma Chemical Co., St. Louis, Mo.

[4] Decadron Elixir, Lot A 3240; Merck Sharp and Dohme.

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Table I—Percentage of Drug Dissolved from Tablets in 30 min in Distilled Water at 37°C Using the USP Rotating Paddle Method at 50 rpm [a]

Tablet	Percentage Dissolved in 30 min [b]
B	93.8 ± 1.9
C	40.2 ± 7.4
D	68.7 ± 7.9
E	7.8 ± 1.1

[a] See Ref. 6. [b] Mean ± *SD*, $n = 12$.

Pharmacokinetic and Statistical Analyses—Individual plasma hydrocortisone profiles were interpreted in terms of Eq. 1 (7):

$$C = \frac{FD}{V}\left(\frac{k_a}{k_a - k_{el}}\right)(e^{-k_{el}(t-t_0)} - e^{-k_a(t-t_0)}) \qquad \text{(Eq. 1)}$$

where C is the concentration of exogenous hydrocortisone in plasma at time t, t_0 is the lag time between drug administration and appearance of exogenous drug in plasma, F is the fraction of the dose (D) that is absorbed, V is the apparent distribution volume of hydrocortisone in the body, and k_a and k_{el} are first-order rate constants for drug appearance in and elimination from plasma, respectively. Cumulative drug absorption profiles were constructed from individual data sets by the method of Wagner and Nelson (8). Model-independent estimates of areas under plasma drug concentration curves from zero to infinite time (AUC) were calculated by the trapezoidal rule, with end correction where necessary (9). Concentrations of hydrocortisone in plasma at each sampling time and all pharmacokinetic values were compared with treatments by analysis of variance for crossover design (10). Differences between individual treatments were examined using Tukey's test (11).

RESULTS

***In Vitro* Dissolution**—The mean percentage dissolution of the four tablet formulations is given in Table I. Tablet B dissolved rapidly, dissolution of this product being virtually complete in 30 min. Dissolution of tablets C and D was somewhat slower than tablet B, while tablet E dissolved even more slowly, over 90% of this product being still intact at 30 min.

***In Vivo* Bioavailability**—The mean plasma levels of exogenous hydrocortisone from the suspension and tablet dosages are given, together with standard deviations, in Table II. The mean plasma profiles are summarized on a semilogarithmic scale in Fig. 1. The results of pharmacokinetic analysis are given in Table III.

Following the suspension dose, plasma hydrocortisone levels reached a mean peak concentration of 311 ng/mL at 0.5 h. Absorption was somewhat slower following the tablet dosages and mean peak levels ranging from 225 to 285 ng/mL were obtained at 1.0–1.5 h postdose. After peak levels had been achieved, plasma levels from all dosages declined monoexponentially to reach mean values of 1.5–3.5 ng/mL at 12 h following the tablet doses, and baseline values following the suspension dose. The suspension dose tended to yield higher plasma hydrocortisone levels compared with the tablets during the initial 30-min postdose period. However there were only minor differences in plasma levels between all dosage forms at times subsequent to this.

The mean cumulative percentage of doses absorbed during 4 h postdose are summarized in Fig. 2 (8). Ninety percent of systemically available drug was absorbed by 1 h following the suspension dose and by 2–3 h from the tablets. The suspension gave rise to significantly higher cumulative absorption compared with tablet E at 0.5 and 1 h, but there were no other significant treatment effects at any other sampling time.

There was considerable variation in some pharmacokinetic parameter values, both within and between treatments (Table III). For example, the mean value of k_a ranged from 0.9 ± 0.4 (*SD*) to 7.2 ± 5.4 h^{-1} for treatments E and A, respectively, with other treatments yielding intermediate values, but significant differences ($p < 0.05$) were observed only between the suspension dose and three of the tablet doses. Interpretation of the k_a values is difficult as they are influenced by the computer-generated values of t_0, which had to be arbitrarily fixed while fitting data from treatment E in order to obtain satisfactory convergence. An additional complication is that hydrocortisone has been shown to obey two-compartment kinetics following intravenous administration (5), so that the numerical value of k_a after oral doses is simultaneously influenced by both distribution and absorption phenomena. The various treatments did not significantly influence the hydrocortisone elimination rate.

Faster absorption of hydrocortisone from the suspension compared with tablets is reflected in high C_{max} and low t_{max} values from treatment A compared with some of the tablet dosages. The higher C_{max} from treatment D compared with treatment E was the only significant difference among tablets for the parameters C_{max} and t_{max}. Tablet E gave rise to somewhat slower

Table II—Mean Plasma Hydrocortisone Levels following Single 20-mg Doses of Treatment A (Suspension) and Treatments B–E (Tablets)

Treatment	Plasma Hydrocortisone, ng/mL												
	10 min	20 min	30 min	45 min	1 h	1.5 h	2 h	3 h	4 h	5 h	6 h	8 h	12 h
A													
Mean	164	291	297	281	260	216	173	113	63.6	41.2	23.2	8.4	—[a]
SD	118	77	57	52	45	42	36	37	24.5	20.3	12.8	7.7	—[a]
B													
Mean	27.3	103	170	219	219	221	210	159	114	67.7	41.9	18.7	3.5
SD	28.5	68	86	76	68	53	53	70	58	43.6	28.6	15.9	5.8
C													
Mean	20.8	96	182	244	250	221	207	144	93	57	35.4	12.2	1.5
SD	25.1	88	113	90	68	37	37	57	40	30	19.0	8.8	5.0
D													
Mean	78	165	221	248	259	233	199	132	83.2	49.6	28.7	10.5	1.5
SD	115	123	99	67	61	48	49	49	39.0	28.0	17.0	9.4	2.9
E													
Mean	8.1	60	132	204	223	230	211	148	91	56.0	34.7	15.9	3.2
SD	14.1	46	86	106	102	71	54	40	36	30.5	18.6	12.9	6.4

[a] Concentration not different from predose, baseline value.

Table III—Hydrocortisone Pharmacokinetic Parameter Values (±1 *SD*)

Parameter	Treatment					Significance[a]	HSD[b]
	A	B	C	D	E		
k_a (h^{-1})	7.2 ± 5.4	2.0 ± 1.2	2.5 ± 2.1	3.9 ± 5.6	0.9 ± 0.4	A > BCE	3.4
k_{el} (h^{-1})	0.53 ± 0.20	0.50 ± 0.13	0.62 ± 0.37	0.54 ± 0.10	0.66 ± 0.22	—[c]	0.17
$t_{1/2,el}$ (h)	1.4 ± 0.3	1.5 ± 0.4	1.3 ± 0.5	1.3 ± 0.3	1.2 ± 0.4	—	0.32
t_0 (h)	0.07 ± 0.08	0.19 ± 0.24	0.21 ± 0.15	0.13 ± 0.13	0.01 ± 0.0[d]	—	0.15
FD/V (ng/mL)	410 ± 118	445 ± 120	425 ± 103	450 ± 87	520 ± 128	E > AC	110
C_{max} (ng/mL)[e]	311 ± 41	252 ± 40	267 ± 46	285 ± 62	225 ± 43	A > BE, D > E	49
t_{max} (h)	0.7 ± 0.2	1.4 ± 0.7	1.2 ± 0.5	1.0 ± 0.6	1.4 ± 0.6	BCE > A	0.41
AUC (ng·h/mL)	800 ± 168	911 ± 234	821 ± 287	858 ± 224	897 ± 204	—	168
r^2[g]	0.98 ± 0.02	0.96 ± 0.05	0.98 ± 0.03	0.99 ± 0.01	0.92 ± 0.06	—	
SS $(ng/mL)^2 \times 10^{-3}$[h]	2.64 ± 2.41	5.82 ± 3.92	3.17 ± 1.63	3.46 ± 2.50	13.5 ± 6.1		

[a] Significant level = 95%. [b] Honestly Significant Difference detectable at $p < 0.05$ (10). [c] No significant differences. [d] The value of t_0 was fixed while fitting treatment E plasma data to Eq. 1 to obtain convergence. [e] Observed maximum concentration of hydrocortisone in plasma. [f] Time of C_{max}. [g] Coefficient of determination, $r^2 = (\Sigma obs^2 - \Sigma dev^2)/\Sigma dev^2$, obtained by fitting individual data to Eq. 1. [h] Deviation sums of squares.

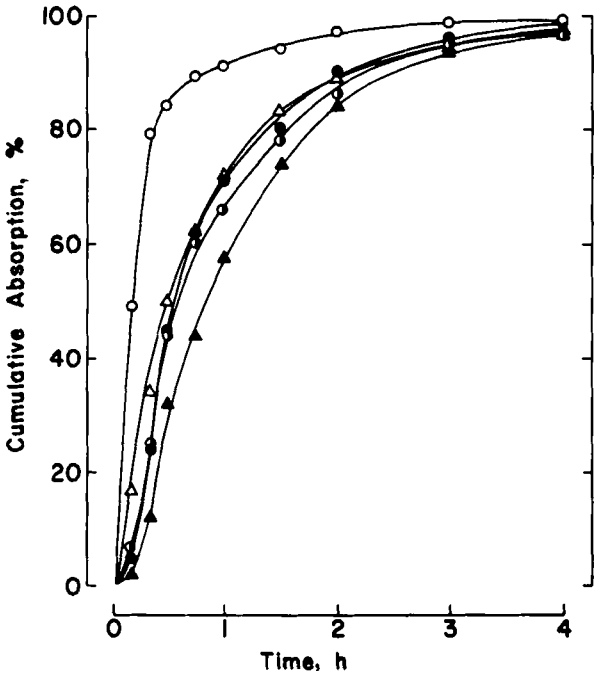

Figure 2—*Mean cumulative percentage of available hydrocortisone dose absorbed by 4 h postdose. Key: (○) suspension A; (◑) tablet B; (●) tablet C; (△) tablet D; (▲) tablet E.*

absorption compared with both the suspension and Tablet D, but the parameter *FD/V*, which is equivalent to the AUC normalized for variations in k_{el}, was significantly higher from treatment E compared with treatments A and C.

The high coefficients of determination for treatments A–D, and also similar deviation sums of squares for these treatments, indicate that individual plasma data sets were adequately described by Eq. 1. Plasma profiles tended to be somewhat more variable from tablet E, and this is reflected in the lower coefficient of determination and greater deviation sums of squares for this tablet formulation. Numerical values for pharmacokinetic values in this study are generally similar to those reported earlier (4, 5).

The HSD values in Table III indicate the difference between parameter values that this study was capable of detecting at the 95% confidence level (10). Comparison of the HSD and parameter values indicates that the study was capable of detecting a 25% difference between treatments at the 95% confidence level for all pharmacokinetic parameters except t_{max}, where a 29% difference could be detected, and k_a and t_0, for which the study was relatively insensitive.

DISCUSSION

Previous studies in this laboratory have suggested that hydrocortisone is ~50–60% available to the systemic circulation following 10–20-mg tablet or suspension doses (4, 5). The results of the present study show that incomplete absorption of hydrocortisone is probably due to intrinsic absorption effects, first-pass hepatic clearance, or both. The similar plasma profiles obtained among tablet dosages, despite a 12-fold range in their dissolution rates, and also similar overall absorption efficiency from the tablet and suspension formulations suggest that dissolution does not play a dominant role in oral hydrocortisone absorption. Our observations with hydrocortisone are similar to those reported earlier for prednisolone and prednisone (12, 13). In those studies, similar plasma profiles for prednisolone were obtained from oral tablet formulations with widely divergent dissolution characteristics in water.

Apart from the discrepancies between products C and E in the value of *FD/V*, and between products D and E in the value of C_{max}, the four tablet products examined here can be considered bioequivalent. However, two of the products (C and E) did not meet the official dissolution requirements for hydrocortisone tablets, *i.e.*, 70% dissolution in 30 min (6). Since completion of the *in vitro* dissolution studies, these products have been reformulated to meet the official requirements[5].

In conclusion, the four hydrocortisone tablet products studied here were bioequivalent. We conclude that other hydrocortisone products meeting the official dissolution test requirement will also be bioequivalent.

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