The trend in the high-affinity association constants, namely, rabbit > human > rat > pig, parallels that observed for nickel binding to the same albumins as determined previously (27). While it was not possible to obtain consistent values for copper binding to dog serum albumin, the results seemed to indicate that the primary binding sites for canine albumin had a lower affinity than those found in porcine albumin. Again, this is the case for nickel binding (27). If both Cu^{2+} and Ni^{2+} occupy the same albumin binding sites and form complexes of the same geometry type, then one would expect the same trend for both copper and nickel binding. This suggests that the *N*-terminal Cu^{2+}-binding site may also constitute the primary binding site for nickel. The relatively lower binding constants for dog and pig albumins are probably due to the absence of a histidine at the third amino acid position from the *N*-terminal end of these proteins (26).

The number of high-affinity sites for human albumin is less than that for bovine (Table I). From a comparison of the proposed primary structures of these proteins (28, 29), and based on the assumption that the geometry at the additional sites should be comparable to that at the *N*-terminal site, two extra high-affinity sites in bovine albumin may be provided by the amino acid sequences of Glu^{16}–Glu–His^{18} near the *N*-terminal and Asp^{373}–Lys–Leu–Lys–His–Leu–Val–Asp^{380} between the second and the third domains. However, it should be pointed out that this assignment is only tentative and needs to be further substantiated experimentally. It is our experience that the extrinsic circular dichroism spectra of bound copper are not the same for human and bovine albumins[10]. Obviously, there must be some significant differences in both the number and the nature of the copper binding sites for these two types of albumin.

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Effect of Dose Size on the Pharmacokinetics of Oral Hydrocortisone Suspension

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Abstract □ The pharmacokinetics of hydrocortisone were examined following single doses of 5-, 10-, 20-, and 40-mg hydrocortisone suspensions to healthy male volunteers. Endogenous hydrocortisone was suppressed by giving 2 mg of dexamethasone the night before hydrocortisone administration. Plasma samples obtained serially for 12 hr after hydrocortisone administration were assayed by reversed-phase high-pressure liquid chromatography using a fixed-wavelength (254 nm) UV absorbance detector. Drug absorption was rapid, with mean maximum plasma hydrocortisone concentrations occurring within 60 min of dosing. Subsequent drug elimination was monophasic with mean elimination half-lives increasing from 1.2 hr for the 5-mg dose to 1.7 hr for the 40-mg dose. Increases in *AUC* and C_{max} with increasing dose were linear but not directly proportional to dose size. This was attributed to dose-dependent absorption or to loss of drug during the first-pass through the liver.

Keyphrases □ Hydrocortisone—effect of dose size on pharmacokinetics of oral suspension, absorption, elimination □ Pharmacokinetics—oral hydrocortisone suspension, absorption, elimination, effect of dose size □ Absorption—oral hydrocortisone suspension, elimination, effect of dose size on pharmacokinetics □ Suspension—oral hydrocortisone, absorption, elimination, effect of dose size on pharmacokinetics

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). A series of studies was initiated to examine the pharmacokinetics of hydrocortisone and to assess the feasibility of conducting bioequivalence studies on commercial products.

In a previous study (2), dexamethasone was shown to

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Table I—Mean Pharmacokinetic Parameter Values[a] Obtained following 5-, 10-, 20-, and 40-mg Oral Doses of Hydrocortisone

Parameter	Value				Statistic[b]
	5-mg Dose	10-mg Dose	20-mg Dose	40-mg Dose	
k_{el}, hr^{-1}	0.60 ± 0.07	0.57 ± 0.01	0.46 ± 0.04	0.42 ± 0.07	$\overline{ABCD}$[c]
$t_{1/2\ el}$, hr	1.2 ± 0.1	1.3 ± 0.2	1.5 ± 0.14	1.7 ± 0.3	$\overline{DCBA}$
C_{max}[d], ng/ml	119 ± 23	175 ± 119	263 ± 55	389 ± 103	$\overline{DCBA}$
t_{max}[d], hr	0.7 ± 0.4	0.8 ± 0.5	0.9 ± 0.5	1.0 ± 0.5	$\overline{DCBA}$
AUC, ng·hr/ml	293 ± 57	447 ± 75	835 ± 148	1340 ± 360	$\overline{DCBA}$
$AUC\ k_{el}$, ng/ml	171 ± 26	248 ± 21	377 ± 44	553 ± 90	DCBA
$AUC\ k_{el}\ D\ 10^{-6}$/ml	34 ± 5	25 ± 2	19 ± 2	14 ± 2	ABCD
C_{max}/D, 10^{-6}/ml	24 ± 5	18 ± 2	13 ± 3	10 ± 3	ABCD

[a] ±1 *SD*. [b] Differences were considered significant at the 95% level. [c] A = 5 mg, B = 10 mg, C = 20 mg, D = 40 mg. [d] Observed values.

suppress endogenous hydrocortisone plasma levels from normal values of 40–200 ng/ml to 6–14 ng/ml for at least 21 hr, thus permitting accurate measurement of circulating exogenous hydrocortisone with negligible interference by endogenous compounds. A reversed-phase high-pressure liquid chromatographic (HPLC) assay for hydrocortisone in plasma, capable of measuring concentrations as low as 5 ng/ml, was used to determine the pharmacokinetics from 10-, 30-, and 50-mg doses of hydrocortisone given as oral tablets to healthy male volunteers (3). Results obtained in this study suggested that hydrocortisone pharmacokinetics may be dose-dependent, and that increases in circulating levels may not be dose-proportional. Similar results to these were observed following oral doses of cortisone acetate (4). A subsequent study, in which 5-, 10-, 20-, and 40-mg doses of hydrocortisone sodium succinate were given intravenously, demonstrated dose-proportional hydrocortisone levels and dose-independence of most pharmacokinetic values (5). Dose-nonproportionality following oral doses was thus attributed either to tablet effects or to nonlinear absorption or first-pass metabolism.

In the present study, hydrocortisone pharmacokinetics were examined in healthy male volunteers following oral doses of 5, 10, 20, and 40 mg of hydrocortisone suspension.

EXPERIMENTAL

Materials—Chemical standard hydrocortisone[1] and internal standard Δ^4-pregnen-17α,20β,21-triol-3,11-dione[1] were analytical grade. Reagent grade methylene chloride[2] was distilled prior to use. 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 and 9 am subsequent to administration of 2 mg of dexamethasone at 11 pm the previous day.

Subjects—After giving informed consent, eight male volunteers (age 22–39 years, height 170–183 cm, weight 64–77 kg) underwent physical examinations including blood and urine analyses. Vital signs and laboratory values for all subjects were normal.

Protocol—Each subject received 5-, 10-, 20-, and 40-mg doses of hydrocortisone as an oral suspension[3] at least 1 week apart in a randomized block design. Subjects were fasted from 10 pm on the day prior to dosing until 12 noon the next day. All subjects received 2 mg of dexamethasone[4] together with 180 ml of water at 11 pm hr on the day before dosing. Hydrocortisone suspension (0.1–0.8 ml) was mixed with 60 ml of orange juice immediately before dosing. The orange juice–hydrocortisone mixture was swallowed, rapidly followed by three 40-ml rinses of orange juice. Dosing containers were assayed for residual hydrocortisone and contained 0.41 ± 0.25% (*SD*) of the dose; this was considered negligible. Subjects were permitted to ingest no other liquid until 4 hr after dosing.

Blood samples (10 ml) were taken from a forearm vein into heparinized vacuum tubes immediately before and then serially from 15 min to 12 hr after hydrocortisone administration. Blood samples were centrifuged immediately and the plasma was stored at −20° until assayed. Subjects were ambulatory during blood sampling.

Assay—The HPLC assay used in this study was described previously (3). Hydrocortisone and added internal standard were extracted from 1 ml of plasma into methylene chloride. The residue from the evaporated organic layer was reconstituted in the liquid chromatographic mobile phase (60% aqueous methanol), and 30 μl was injected onto the column. Components were detected at 254 nm, and concentrations of hydrocortisone were calculated by peak height ratio. Separate standard curves were run with each batch of samples. Suppressed hydrocortisone concentrations obtained just before hydrocortisone administration were subtracted from all concentrations obtained after dosing for each subject.

Data Analysis—Model-independent estimates of areas under plasma hydrocortisone concentration curves from zero to infinite time (AUC) were calculated by trapezoidal rule, with end correction where necessary (6). Elimination rate constants were calculated by regression analysis of the postabsorption phase of hydrocortisone plasma profiles.

Pharmacokinetic parameters were examined by ANOVA for crossover design. Differences between individual doses were analyzed using Tukey's test (7).

RESULTS

Mean plasma hydrocortisone concentrations, corrected for endogenous hydrocortisone, are shown for all four dose levels in Fig. 1. Drug absorption was rapid, with maximum drug concentrations occurring within 1 hr of dosing. Drug levels then declined monoexponentially in all cases. Mean hydrocortisone levels resulting from the 10-, 20-, and 40-mg doses were slightly elevated at the last sampling times, suggesting the possibility of a more prolonged terminal elimination phase. However, the drug levels at these times approached the lower sensitivity limit of the assay, so that their significance is uncertain. This effect was not noted following the 5-mg dose. Exclusion of the terminal data points did not significantly affect the calculated drug half-lives. Hydrocortisone concentrations were above predose suppressed values for up to 8 hr following the 5- and 10-mg doses, and up to 12 hr following the 20- and 40-mg doses.

Pharmacokinetic parameters and statistical analysis are presented in Table I. Mean peak levels of hydrocortisone increased from 119 ng/ml following the 5-mg dose, to 389 ng/ml following the 40-mg dose. The time of peak levels was independent of dose. The elimination half-life was affected by dose size, increasing from a mean value of 1.2 hr following the 5-mg dose to 1.7 hr following the 40-mg dose. The area under the hydrocortisone plasma curve, and also the area corrected for variance in the elimination rate constant, $AUC\ k_{el}$, both increased with increasing dose. However, the increases in both the area and C_{max} values were not dose-proportional. Doubling the dose at 5, 10, and 20 mg resulted in mean area increases of 1.5-, 1.9-, and 1.6-fold, respectively, while the value of C_{max} increased 1.5-fold with each two-fold increase in dose.

The nonproportional relationship between AUC, C_{max}, and dose size is shown graphically in Fig. 2. Linear regression analysis resulted in positive y-intercepts which were significantly >0 ($p < 0.05$). When $AUC\ k_{el}$ and C_{max} values were corrected for dose size (Table I) the resulting values significantly decreased between each incremental dose of hydrocortisone.

DISCUSSION

In this study, the pharmacokinetics of hydrocortisone have been described following 5-, 10-, 20-, and 40-mg oral suspension doses to healthy

[1] Sigma Chemical Co., St. Louis, MO 63178.
[2] Burdick and Jackson Laboratories, Muskegon, MI 49442.
[3] Cortef intramuscular suspension, 50 mg/ml, Upjohn, Kalamazoo, MI 49001.
[4] Decadron elixir, 0.1 mg/ml, Merck, Sharp and Dohme, West Point, PA 19486.

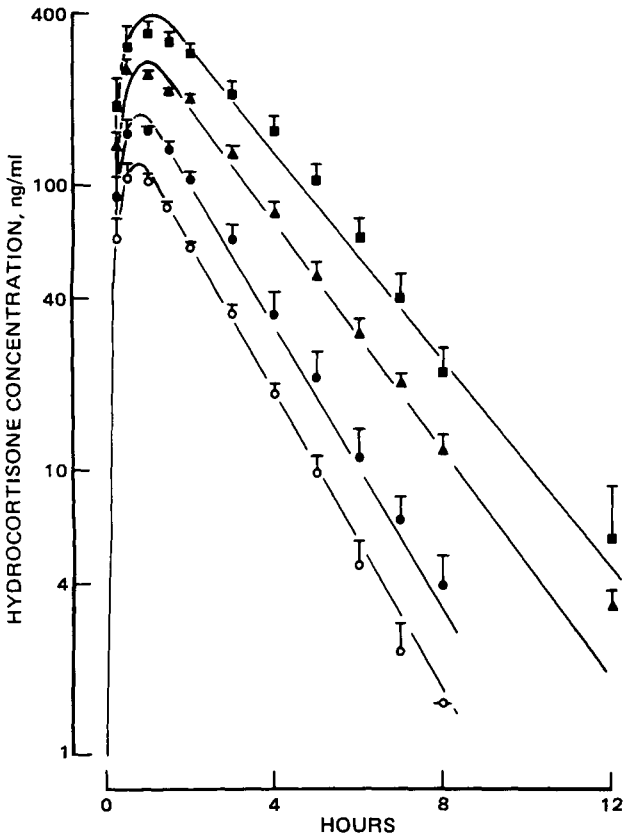

Figure 1—*Mean plasma hydrocortisone concentrations (±1 SEM, n = 8) versus time for subjects receiving oral hydrocortisone suspensions. Key: (○) 5 mg; (●) 10 mg; (▲) 20 mg; (■) 40 mg.*

volunteers. The plasma profiles, and also the values of pharmacokinetic parameters, obtained under these conditions are generally consistent with values reported elsewhere (8–12). The drug is absorbed rapidly into the circulation, achieving peak plasma concentrations within 1 hr. Plasma levels then decline with a half-life of 1.2–1.7 hr. The plasma levels of hydrocortisone obtained in this study are comparable to those obtained previously when a tablet dosage form was used (3). The only dose size that was common to both studies, 10 mg, yielded almost identical C_{max} and *AUC* values.

Increases in circulating levels of hydrocortisone have thus been shown not to be proportional to increasing doses following both tablet (3) and suspension dosage forms. An overall five-fold increase in the tablet dose (10–50 mg) resulted in a 2.1-fold increase in mean C_{max}, and a 3.3-fold increase in *AUC* values. In the present study an overall eight-fold increase in the suspension dose (5–40 mg) resulted in a 3.3-fold increase in C_{max} and a 4.6-fold increase in *AUC*. The somewhat greater increase in *AUC* compared to C_{max} with increasing dose in both studies is due to the somewhat slower absorption and elimination of hydrocortisone at higher doses resulting in flatter and somewhat more prolonged drug profiles.

A number of explanations was originally proposed to account for the nonproportional relationship between circulating hydrocortisone levels and the size of the oral dose (3). These included changes in the binding characteristics of hydrocortisone to plasma proteins, limited tablet dissolution, saturable absorption, and an increased first-pass effect following higher doses. Of these, changes in binding characteristics appear unlikely as plasma levels of hydrocortisone have been shown to be dose-proportional following those intravenous doses that yielded similar circulating drug levels to those obtained following the oral doses (5). Limited tablet dissolution at higher doses is also an unlikely explanation as similar effects occurred with both tablet and suspension dosages.

It is difficult to distinguish the other possibilities, limited absorption and greater first-pass metabolism, from the present data. Previous studies have indicated that hydrocortisone is well-absorbed from the small intestine (13), and absorption appears not to be saturable at dosages used in the present study (14). Dividing the mean *AUC* values obtained following the suspension dose by those obtained after equivalent intravenous doses (5) shows that the systemic availability of hydrocortisone is 71, 57, and 56% from the 5-, 10-, and 20-mg doses, respectively. Similar

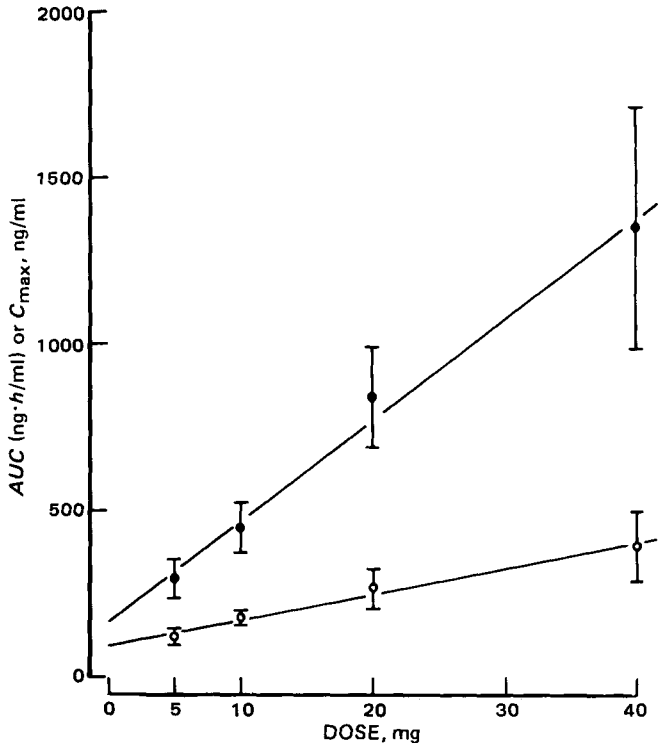

Figure 2—*Relationship between mean (±1 SD) AUC and C_{max} values, and oral hydrocortisone dose (n = 8). Key: (●) AUC; (○) C_{max}.*

comparison of the tablet dose data indicates that systemic availability of hydrocortisone was 60% from a 10-mg dose, and 40% from 30- and 50-mg doses.

In the absence of additional information, the most likely cause of the apparent dose dependency of hydrocortisone absorption is that of increased first-pass metabolism at higher doses. The rapid absorption of hydrocortisone from the GI tract will give rise to transient, high drug levels in the splanchnic circulation. These levels are likely to exceed the binding capacity of the high-affinity, low-capacity binding protein transcortin (15), resulting in a large proportion of drug passing through the liver during the first-pass either loosely bound to the low-affinity, high-capacity protein albumin or in free form. The percentage of drug that is in the loosely bound or unbound form during the first-pass will increase, while the percentage of drug tightly bound to transcortin will decrease, as the size of the dose increases. An increased free fraction during the first-pass is likely to permit greater hepatic clearance, and to decrease the overall systemic availability of unchanged drug. While this hypothesis is attractive, further studies are needed to identify the intrinsic relationships between the protein binding and hepatic clearance of hydrocortisone.

The results obtained in the present study have confirmed that plasma levels of oral hydrocortisone are not proportional to the administered dose. However, as peak plasma levels and *AUC* are approximately linearly related to dose size within the dosage range studied (Fig. 2), we conclude that meaningful bioavailability comparisons can be made for hydrocortisone at therapeutic dose levels.

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COMMUNICATIONS

The Effect of Thermal History on the Transition Temperature of Citric Acid Glass

Keyphrases □ Transition temperature—effect of thermal history, citric acid glass □ Citric acid glass—effect of thermal history on the transition temperature

To the Editor:

Glass is a noncrystalline solid which does not exhibit long-range order of its molecules and has a characteristic temperature where its physical state changes from a rigid, brittle material to a flexible, rubbery material. In addition, glass is not thermodynamically stable and will readily revert to the crystalline state under the proper environmental conditions (1, 2). As a result of these characteristics, materials capable of glass formation have been suggested as vehicles for solid dispersion systems, because it has been theorized that they should exhibit more rapid dissolution than their crystalline counterparts (3–5).

One compound often mentioned as a potential vehicle is citric acid (6–12). In the crystalline state, this material is highly hydrogen bonded (13), a property that apparently is responsible for its glass formation, because it has been reported that hydrogen bonding tendency helps prevent crystallization from occurring when a liquid melt is cooled below its liquidus temperature (14–16).

Recently, there has been a reported discrepancy in the transition temperature (T_g) of citric acid glass. This discrepancy was explained (17) to be due to residual moisture contamination in the samples. These studies (7–10) utilized citric acid monohydrate, while another study (12) employed anhydrous citric acid.

We do not dispute this explanation of the discrepancy. However, we thought it would be helpful to future investigators if the effect of thermal history of the melt and the presence of impurities on the T_g of citric acid glass was reported.

Anhydrous citric acid[1] was used in this study in order to eliminate possible effects of residual moisture contamination. The procedures used for sample preparation and determination of the T_g of a glass by differential scanning calorimetry (DSC) have already been discussed in detail (12). In examination of the effect of the thermal history of the molten citric acid on the T_g of citric acid glass, the DSC procedure was modified such that after heating the citric acid to melting, the molten citric acid was raised to the desired temperature and held isothermally for a specified time before rapidly being cooled.

Table I—The Transition Temperatures Obtained for Citric Acid Glass after Holding Molten Citric Acid Isothermally above Its Melting Temperature for Specified Times

Temperature°	Time, min	T_g Values°
172	5	10.0[a]
	15	7.0
	30	2.0
177	5	10.0
	20	4.0
180	5	8.0
	15	3.0
	30	0.0
190	5	6.5
	15	1.0
	30	—[b]

[a] Average of at least duplicate determinations. [b] Material discolored, not able to detect a T_g from −60 to 200°.

Table I shows the effect of thermal history on the T_g of citric acid glass. Results indicate that the higher the temperature and the longer the exposure time at a given temperature, the lower the T_g value of citric acid glass. Accompanying this decrease in the T_g value was a progressive discoloration of the molten citric acid from a clear transparent liquid to a yellowish brown liquid.

Aconitic acid[2], a dehydration decomposition product of citric acid, degrades upon melting. By adding the material to citric acid in varying proportions and then preparing glass dispersions of the mixture, it is possible to simulate the effect of degradation product impurities on the T_g of citric acid glass. Figure 1 shows that as the level of impurities increases, the T_g of citric acid glass decreases.

The thermal stability of citric acid has been of concern to previous solid dispersion investigators (6–10, 12). Available thermal analysis literature on citric acid is limited. One study (18) suggests that citric acid may begin to decompose at ~185°, while another study (19) states that thermal degradation of citric acid does not begin to occur until 200–225°. The data presented in this communication indicate that citric acid does exhibit some degree of thermal instability. However, thermal degradation does not appear to begin immediately upon initial melting but only

[1] J. T. Baker Chemical Co., Phillipsburg, N.J.

[2] Aldrich Chemical Co., Milwaukee, Wis.

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