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Protein Binding of Clindamycin in Sera of Patients with AIDS

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Patients with AIDS have altered pharmacokinetics of clindamycin compared with those of healthy control subjects. In an attempt to better understand these differences, we undertook a study of protein binding of clindamycin in sera of patients with AIDS. Fifteen patients with AIDS and 15 healthy volunteers were given a single 600-mg dose of clindamycin orally and intravenously, and serum samples were collected at three time points corresponding to high, midpoint, and low clindamycin concentrations. Protein binding was determined by ultrafiltration, and total and unbound clindamycin concentrations were measured with a gas chromatography assay. AIDS patients had α_1-acid glycoprotein values approximately twice those of healthy volunteers (mean ± standard deviation, 103 ± 27 versus 61 ± 11 mg/dl; $P = 0.001$). Overall, serum protein binding levels were higher in AIDS patients (mean ± standard deviation, 83 ± 7 versus 78% ± 8%; $P = 0.0001$), which is likely the result of increased α_1-acid glycoprotein levels in these patients. Total concentrations of clindamycin in plasma were significantly higher in AIDS patients at most time points studied, while unbound serum clindamycin concentrations did not differ among the groups at each sampling time after both oral and intravenous dosing. Increased protein binding may partly explain the altered pharmacokinetic disposition of clindamycin in AIDS patients; however, other factors cannot be excluded.

Clindamycin is an effective alternative for treatment of *Pneumocystis carinii* pneumonia and toxoplasmic encephalitis in patients with AIDS, particularly when allergy or intolerance to sulfonamides is encountered (4, 14, 18). In a previous investigation, we found that the pharmacokinetic disposition of clindamycin is altered in patients with AIDS compared with that in healthy control subjects (6). AIDS patients showed significantly greater bioavailability, lower plasma drug clearance, and a smaller steady-state volume of distribution (6). The reasons for the observed differences in clindamycin disposition are unknown and could include altered binding of protein in serum or tissue, altered intrinsic clearance, or other factors relating to the disease state.

Previous studies have shown clindamycin to be highly bound to serum proteins (80 to 95%), primarily to α_1-acid glycoprotein (AAG), an acute-phase protein (7, 8, 11, 17). Increased synthesis of AAG occurs in response to stress, including infection, burn injury, surgery, and myocardial infarction (8, 11, 19). Furthermore, AAG concentrations have been shown to remain persistently elevated in chronic conditions, such as malignancy, rheumatoid arthritis, chronic pain, and uremia (3, 11). Elevated AAG concentrations have been described for patients with AIDS, with no substantial change noted after 2 to 3 months of zidovudine therapy (15). Given that levels of AAG in serum are elevated in patients with AIDS, increased binding of basic drugs such as clindamycin is likely to occur. Increased binding related to increased AAG concentrations has been demonstrated in vitro for clindamycin in uremic serum (2) and for azithromycin in sera obtained from patients with burns, myocardial infarction, surgery, cancer, and trauma (20). Alterations in protein binding can influence both the pharmacokinetics (e.g., tissue penetration) and pharmacodynamics (e.g., biological activity at the site of infection) of antimicrobial agents (1, 3); therefore, the present study was undertaken to evaluate protein binding of clindamycin in sera from patients with AIDS.

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MATERIALS AND METHODS

Subjects. Serum samples from 30 of the 32 subjects enrolled in the pharmacokinetic study (6) were collected for protein binding determination. This group included 15 male patients with AIDS (mean [± standard deviation; SD] age, 35.2 ± 6.5 years; weight, 75.7 ± 9.3 kg) and 15 healthy male volunteers (mean [± SD] age, 26.9 ± 3.9 years; weight, 72.3 ± 12.9 kg). Prior to enrollment, all subjects gave written informed consent as required by the Committee on Human Research at the University of California, San Francisco. In the patient group, the diagnosis of AIDS was based on the presence of human immunodeficiency virus (HIV) seropositivity and a history of opportunistic infection, which was the definition used by the Centers for Disease Control at the time the study was initiated. CD4 lymphocyte counts were not obtained and thus were not considered in the AIDS diagnosis.

Twelve of the 15 AIDS patients were taking zidovudine at the time of participation in the study. Six patients took chronic acyclovir therapy for suppression of herpes simplex virus infection, 10 received aerosolized pentamidine, 2 received megestrol to promote weight gain, and 2 patients occasionally took nonsteroidal anti-inflammatory agents (ibuprofen and naproxen [1 patient each]) for pain. One patient reported taking famotidine. Healthy volunteers were not allowed to take any medications. AIDS patients with active gastrointestinal, hepatic, renal, or neurologic diseases or those with active opportunistic infections were excluded from the study.

Clinical and laboratory monitoring of study subjects was performed as previously described (6). Briefly, each subject was required to provide a complete medical history and undergo a physical examination and a panel of laboratory tests consisting of a complete blood cell count with differential and platelet count, urinalysis with microscopic analysis, and serum chemistry analysis prior to enrollment and upon completion of the study. Values for healthy volunteers were required to be within the normal range. For AIDS patients, the following exceptions were permitted: alanine aminotransferase or aspartate aminotransferase concentration $\leq$2.3 times the upper limit of the normal range, serum bilirubin concentration $\leq$1.5 times the upper limit of the normal range, leukocyte count $\geq 2.4 \times 10^3$ cells per mm^3, and erythrocyte count $\geq 3 \times 10^6$ cells per mm^3. Serum albumin concentrations were determined for all subjects at the time of enrollment, and serum AAG levels were determined on two separate occasions immediately prior to oral and intravenous (i.v.) dosing. AAG concentrations were measured with a radial immunodiffusion assay (NOR-Partigen AAG kit; Behring Diagnostics, Inc., Somerville, N.J.).

TABLE 1. Demographic data for the subjects in this study

Group	Age (yr)	Wt (kg)	Albumin concn (g/dl)	AAG concn	
				i.v.[a]	Oral[b]
Healthy volunteers					
Mean ± SD	26.9 ± 3.9	72.3 ± 12.9	4.9 ± 0.3	61.0 ± 10.6	56.9 ± 11.9
Range	22–35	55.8–102.0	4.5–5.4	38.4–78.9	38.3–83.4
AIDS patients					
Mean ± SD	35.2 ± 6.5	75.7 ± 9.3	4.3 ± 0.4	103.3 ± 26.7[c]	102.9 ± 35.5[c]
Range	25–44	58.1–93.0	3.4–4.8	64.0–146.1	55.9–159.4

[a] AAG concentration determined prior to i.v. administration.
[b] AAG concentration determined prior to oral administration.
[c] $P = 0.001$.

Drug administration. The clinical study was performed in the Clinical Research Unit of the Division of Clinical Pharmacy at the University of California, School of Pharmacy. Each study group received the following treatment assignments separated by at least 1 week in a randomized fashion: treatment A, a single oral dose of clindamycin hydrochloride (Cleocin HCl, lot number 24,814; The Upjohn Company, Kalamazoo, Mich.) at 600 mg (administered as two 300-mg capsules); and treatment B, a single dose of clindamycin phosphate (Cleocin phosphate, lot numbers 605PK and 664PK; The Upjohn Company) at 600 mg administered i.v. in 50 ml of 5% glucose in water as a 25-min infusion. All subjects were required to fast for 10 h before and 2 h after receiving i.v. and oral drug administration. Standard meals were provided during each study day. Subjects abstained from alcohol consumption for 2 days before and during each study day. No caffeine-containing beverages were allowed for 1 day before and during each study day.

Sample collection. Blood samples (7 ml each) were collected for serum protein binding analysis after each of the treatment regimens at three separate time points representative of early, midpoint, and later concentration values. With treatment A, blood samples were obtained prior to (zero hour) and 1, 2, and 6 h after the oral dose. With treatment B, blood samples were collected prior to (zero hour) and 0.5, 2, and 6 h after the start of the i.v. infusion. Each sample was collected into a Vacutainer tube (Becton Dickinson Systems, Rutherford, N.J.) containing no additives. Samples were allowed to clot, placed on ice, and centrifuged within 30 min of collection. Serum was harvested and stored at −80°C until clindamycin protein binding analysis was performed. Total clindamycin concentrations (C_{tot}; i.e., the bound concentration [C_b] and the unbound concentration [C_u]) in plasma were determined at the same time points as previously described (6). Seven milliliters of blood was collected into a heparin-containing Vacutainer tube (Becton Dickinson Systems), placed on ice, and centrifuged within 30 min of collection. Harvested plasma was stored at −80°C until assayed for C_{tot}.

Analytical methods. Clindamycin concentrations were determined by a capillary gas-liquid chromatographic assay procedure as previously described (6). Clindamycin hydrochloride and a structural analog used as the internal standard (U-33232E) were provided by the The Upjohn Company. In brief, samples were prepared by liquid-liquid partitioning with back extraction (ethyl acetate at basic pH followed by water at acidic pH and then chloroform at basic pH) and derivatization with heptafluorobutyric anhydride. The final clindamycin derivative was injected into an HP5890 gas chromatograph equipped with an automatic injector, W-17 fused-silica capillary column, and electron capture detector. Helium (zero grade) (LCCO, Chicago, Ill.) was used as the carrier gas (flow rate, ≈2 ml/min), with nitrogen (zero grade) (LCCO) as the make up gas (flow rate, 35 to 40 ml/min). The injector and detector temperatures were 225 and 350°C, respectively. A two-step temperature gradient (165 to 200°C, and then 200 to 250°C) was employed. Interday variability and intraday variability were 8.2 and 3.2%, respectively, at a concentration of 75 ng/ml ($n = 9$). The levels of accuracy of the assay procedure were 3.9 and 6.9% at concentrations of 75 ($n = 9$) and 350 ($n = 9$) ng/ml, respectively. Inactivation of HIV in serum was not performed, because preliminary experiments showed that the procedure (heat deactivation at 56 to 58°C for 35 to 45 min) substantially affected determination of C_u. No interference with concomitant medications taken by AIDS patients was detectable by comparison of predose plasma sample chromatograms.

Serum protein binding of clindamycin was determined by ultrafiltration with the Amicon Centrifree system (Amicon Corporation, Danvers, Mass.). Serum samples were bubbled with CO_2 to a target pH of 7.3, and 1.0 ml of serum was added to the ultrafiltration device and allowed to equilibrate for approximately 30 min on a rotor prior to centrifugation. In situations in which <1.0 ml of serum was available, the entire sample was added to the ultrafiltration device, and then the concentration in the ultrafiltrate was adjusted to the initial volume of serum used. Samples were filtered at 2,500 rpm for 20 min at 37°C. Ultrafiltrate was recovered, and 100 or 200 μl was then taken to a total volume of 1.0 ml with Krebs-Ringer buffer prior to the gas chromatography assay to determine the C_u. Samples were batched during assay runs to achieve a balance between groups (e.g., AIDS patient 1 and healthy volunteer 1, etc.). Binding of clindamycin to the ultrafiltration membrane was evaluated at three concentration levels. The mean rates of recovery of clindamycin were 100.5% at 15 μg/ml, 95.8% at 7 μg/ml, and 89.8% at 1 μg/ml.

Analysis of data. The fraction bound [F_b] was determined by the equation $F_b = (C_{tot} - C_u)/C_{tot}$. The percent protein binding was then calculated by multiplying F_b by 100. Serum AAG, C_{tot}s, and C_us and percent protein binding values for AIDS patients were compared with those observed for healthy volunteers by the Mann-Whitney U test. Percent serum protein binding values were correlated with serum AAG levels by linear regression. For all comparisons, $P < 0.05$ was considered significant.

RESULTS

The demographic data for both study groups are listed in Table 1. The patients with AIDS were an average of 8 years older than the healthy volunteers, but they had similar body weights. Mean serum albumin values were slightly higher in the healthy volunteers, although the difference was not significant. In contrast, patients with AIDS showed significantly higher AAG values than healthy subjects, and the patients also exhibited greater variability in AAG levels ($P = 0.001$ [Table 1]). In the group of AIDS patients, AAG concentrations ranged from 55.9 to 159.4 mg/dl, and similar mean results were obtained on the two occasions on which AAG was determined. AAG levels were, on average, 40 to 50% lower in healthy volunteers than in AIDS patients, with the highest AAG concentration in healthy volunteers being 83.4 mg/dl. As in the group of AIDS patients, similar AAG values were observed in the healthy volunteers during both collection times.

Plasma C_{tot}s and serum C_us after i.v. and oral administration are given in Tables 2 and 3. In general, plasma C_{tot}s were higher in AIDS patients than in healthy volunteers at all three sampling times after i.v. administration; however, a significant difference was only found at the 2-h sampling time point (Table 2). After oral administration, plasma C_{tot}s were approximately 1.5 times higher in AIDS patients than in healthy volunteers, achieving statistical significance at each of the three sampling times (Table 3). In contrast, C_us were not significantly different among the groups at any of the time points studied (Tables 2 and 3).

Clindamycin protein binding results after i.v. and oral administration are given in Table 4. At the concentrations achieved in the study subjects, serum protein binding ranged from 73 to 85% and did not demonstrate any noticeable concentration dependency. The overall protein binding levels (mean ± SD) were 83.0% ± 7.3% (range, 61.4 to 92.5%) and 78.3% ± 8.2% (range, 54.3 to 89.4%) for patients with AIDS and healthy volunteers, respectively ($P = 0.0001$). Except for the 0.5-h time point with i.v. administration, mean protein binding values were consistently higher at each sampling time in AIDS patients than in healthy volunteers (Table 4), and

TABLE 2. C_{tot} and C_u after i.v. administration of 600 mg of clindamycin

Group (no. of patients or volunteers)	Mean (± SD) C_{tot} (μg/ml) at time (h) postdose			Mean (± SD) C_u (μg/ml) at time (h) postdose		
	0.5	2.0	6.0	0.5	2.0	6.0
AIDS patients (15)	11.7 ± 2.4	6.9 ± 1.7	2.1 ± 1.0	2.6 ± 0.7	1.2 ± 0.6	0.32 ± 0.11
Healthy volunteers (15)	10.4 ± 2.8	5.5 ± 0.8	1.5 ± 0.5	2.3 ± 0.7	1.1 ± 0.3	0.43 ± 0.21
P	0.127	0.035	0.093	0.135	0.778	0.406

considerable variability in both study groups was observed. A more consistent and pronounced increase in protein binding occurred after oral dosing in AIDS patients compared with in healthy volunteers, with results averaging approximately 6% higher at each of the time points studied. When serum protein binding values for subjects in both study groups were plotted versus serum AAG levels, a reasonable correlation was observed (Fig. 1).

DISCUSSION

We have previously demonstrated that compared with healthy volunteers, AIDS patients showed higher bioavailability (75 versus 53%; $P = 0.002$), lower plasma drug clearance (0.21 versus 0.27 liter/h/kg of body weight; $P = 0.014$), and a smaller steady-state volume of distribution (0.66 versus 0.79 liter/kg; $P = 0.005$). The reasons for these differences are unclear, and the differences could be due in part to altered serum protein binding. We have shown that AIDS patients given single oral and i.v. doses of clindamycin do exhibit higher levels of serum protein binding than healthy volunteers.

We have demonstrated elevated serum AAG values in patients with AIDS compared with those in healthy volunteers and observed similar concentrations when AAG was determined on two separate occasions separated by at least 1 week. Depending on the method used, normal AAG values in serum are reported to range from 50 to 100 mg/dl (11). AAG concentrations in the group of AIDS patients included in this study averaged 103 mg/dl, roughly twice that observed in healthy volunteers. Øie et al. evaluated serum AAG concentrations in a group of 23 AIDS patients receiving zidovudine (as participants in AIDS Clinical Trials Group Protocol 020) and in a control group consisting of 6 healthy subjects (15). In their study, AAG levels were, on average, 50 to 60% higher in the AIDS patients than those in the control subjects (25.7 versus 16.2 μM), and they remained elevated to a similar extent after 8 to 12 weeks of zidovudine treatment (15). Thus, on the basis of our results and those of Øie et al., it is apparent that AIDS is another chronic illness associated with elevated concentrations of AAG. Whether further increases in AAG concentrations, beyond those found in our study, occur in AIDS patients with active opportunistic infections such as *P. carinii* pneumonia and toxoplasmic encephalitis, is presently unknown. Because many basic drugs bind to AAG, increases in the levels of this serum protein could have important therapeutic implications, particularly for agents like clindamycin, which are normally highly protein bound.

We found C_{tot}s in plasma to be higher in patients with AIDS than those in healthy volunteers, which was most significant when the drug is given orally. However, C_us were not significantly different among the groups at any of the time points after oral and i.v. administration (Tables 2 and 3). This dichotomy is likely explained by the increased degree of serum protein binding observed in patients with AIDS (Table 4). We have previously demonstrated that the absolute bioavailability of clindamycin is increased in patients with AIDS (75 versus 53%; $P = 0.002$); however, the results from the present study suggest that this does not result in a proportional increase in C_us in this patient population. The C_u (regarded to be the microbiologically active form) approaches or exceeds the MIC for most susceptible bacteria for at least 2 h after dosing in both study groups. However, by 6 h, these concentrations were below the MICs for organisms such as *Staphylococcus aureus* and *Bacteroides fragilis* (13). For severely ill patients, higher i.v. doses (e.g., 600 to 900 mg every 6 to 8 h) are given, which is likely to result in increased concentrations of unbound drug (5). Conversely, when clindamycin is used for oral treatment of bacterial infections (e.g., 300 mg three to four times daily), C_us even lower than those observed in our study would be expected. The precise relationship between concentration and antibacterial effect has not been fully elucidated for clindamycin. Even less information is available regarding concentration-effect relationships in parasitic infections such as toxoplasmic encephalitis and *P. carinii* pneumonia.

This is the first study to evaluate clindamycin serum protein binding in vivo. Patients with AIDS demonstrated significantly higher serum protein binding levels than those in healthy subjects (Table 4). The values we obtained are lower than those of Gordon et al., who reported 94% protein binding for clindamycin when evaluated at a concentration of 5 μg/ml in pooled serum obtained from healthy volunteers (7). The different methodology used (in vitro evaluation with vacuum ultrafiltration and bioassay of ultrafiltrate) may explain why these results differ from ours. Kays et al. evaluated clindamycin protein binding ex vivo, by using sera obtained from patients who recently underwent surgery or those with a history of trauma or myocardial infarction and sera obtained from a group of healthy control subjects (10). Clindamycin protein binding was

TABLE 3. C_{tot} and C_u after oral administration of 600 mg of clindamycin

Group (no. of patients or volunteers)	Mean (± SD) C_{tot} (μg/ml) at time (h) postdose			Mean (± SD) C_u (μg/ml) at time (h) postdose		
	1.0	2.0	6.0	1.0	2.0	6.0
AIDS patients (15)	6.8 ± 2.1	5.5 ± 2.2	1.8 ± 1.0	0.90 ± 0.23	0.76 ± 0.25	0.25 ± 0.11
Healthy volunteers (15)	4.6 ± 1.5	3.5 ± 1.2	0.9 ± 0.5	0.88 ± 0.25	0.70 ± 0.31	0.20 ± 0.06
P	0.004	0.014	0.026	0.520	0.344	0.805

TABLE 4. Serum protein binding results for clindamycin after i.v. and oral administration

Group (no. of patients or volunteers)	Mean (± SD)% serum protein binding at time (h) after i.v. dose			Mean (± SD)% serum protein binding at time (h) after oral dose		
	0.5	2.0	6.0	1.0	2.0	6.0
AIDS patients (15)	76.6 ± 10.0	82.6 ± 5.8	81.5 ± 8.6	85.2 ± 4.5	85.2 ± 4.9	84.0 ± 5.3
Healthy volunteers (15)	77.6 ± 7.8	79.8 ± 5.3	73.3 ± 8.7	79.5 ± 6.8	79.0 ± 8.2	77.7 ± 6.9
P	0.977	0.045	0.022	0.021	0.017	0.095

found to vary, depending upon the drug concentration used and the level of AAG measured in serum. Overall, mean levels of serum binding were 61, 78, and 89% at concentrations of 10, 4, and 2 μg of clindamycin per ml, respectively. At 2 μg/ml, protein binding ranged from 81% in sera containing AAG levels between 100 and 150 mg/dl to 92% at AAG concentrations >200 mg/dl. A similar trend was seen when binding was evaluated at a clindamycin concentration of 4 μg/ml (10). In the present investigation, we observed 82 to 84% protein binding in AIDS patients (whose AAG levels averaged 103 mg/dl) 6 h after oral or i.v. administration (Table 4), at which time C_{tot}s averaged approximately 2 μg/ml (Tables 2 and 3). However, in contrast to the findings of Kays et al., we did not observe any consistent trend toward concentration dependence in serum binding. Even at the highest concentrations we observed (approximately 11 μg/ml), clindamycin protein binding averaged approximately 77% in both groups (Table 4). Importantly, the values obtained in our study are more directly reflective of the dynamic nature of the interaction between drug and serum protein in vivo than those of other studies.

A number of investigators have demonstrated a correlation between drug protein binding and serum AAG concentrations. Kays et al. found that the highest degree of clindamycin protein binding (89 to 92%) occurred when AAG levels were markedly elevated (≥200 mg/dl), which has also been reported by others (2, 3). Craig et al. noted levels of clindamycin protein binding in sera obtained from uremic patients (92%) significantly higher than those in sera from healthy subjects (83%), which correlated with AAG concentrations approaching 300 mg/dl in this patient population (2). Importantly, increased protein binding in uremic patients compared with that in healthy subjects results in higher total, but comparable C_us. This suggests that clindamycin dosing should not be reduced in patients with end-stage renal disease, as has been recommended (9, 16). White et al. have recently demonstrated a four-fold increase in azithromycin protein binding as AAG concentrations in serum are increased (20). A significant increase in azithromycin protein binding was observed when determined by ultrafiltration of sera containing AAG concentrations <100 mg/dl compared with those in sera containing AAG at ≥200 mg/dl (11 versus 40%; $P = 0.047$) (20). Although serum AAG concentrations increased to only a modest extent in the AIDS patients we studied, a significant correlation between serum protein binding values and AAG concentrations did occur (Fig. 1). Whether further increases in AAG with corresponding changes in clindamycin protein binding occur in AIDS patients with active opportunistic infections (or those with concurrent malignancy) is presently unknown and is deserving of further study.

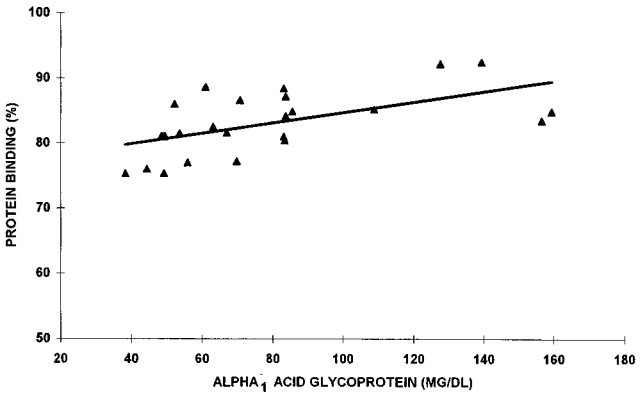

FIG. 1. Correlation between the concentration of AAG in serum and the percentage of protein binding of clindamycin in serum (coefficient of correlation = 0.588; $y = 0.081x + 76.6$; $n = 25$; $P = 0.002$). Serum protein binding values were determined 1 h after a 600-mg oral dose of clindamycin in healthy volunteers and patients with AIDS.

Our results may at least partially explain the differences in clindamycin pharmacokinetics found in AIDS patients. The higher degree of protein binding in AIDS patients translates into an unbound fraction of approximately 17% versus 22% in healthy volunteers, representing a 23% reduction. Such a reduction in the unbound fraction may partially explain the smaller volume of distribution at steady state we observed in AIDS patients compared with that in healthy volunteers (0.66 versus 0.79 liter/kg, respectively; $P = 0.005$) (6). Although we failed to observe any significant differences in C_us among the two groups, it is also possible that in AIDS patients, higher levels of protein binding result in less drug available to be cleared by the liver. This could potentially explain the 22% reduction in plasma clearance we observed in AIDS patients (6), although altered intrinsic clearance cannot be excluded. Higher-than-normal serum clindamycin concentrations have been reported for hospitalized patients with markedly elevated serum transaminase levels (21). Given that the patients with AIDS in our study had aspartate aminotransferase and alanine aminotransferase values ≤2.3 times normal and also possessed normal prothrombin times and serum albumin concentrations, reduced plasma clearance due to altered hepatic function seems less likely. However, by using caffeine as a probe of oxidative drug metabolism, Lee et al. found altered drug metabolism in HIV-infected patients compared with that in healthy control subjects (12). Caffeine metabolism was reduced most substantially in AIDS patients with acute infection (*P. carinii* pneumonia) compared with that in asymptomatic HIV-positive individuals or healthy volunteers (12).

In conclusion, the serum protein binding of clindamycin in AIDS patients was evaluated and was found to be, on average, 6% higher than that observed in healthy volunteers. The difference is likely the result of increased AAG levels found in patients with AIDS. At the three time points included in this study, no significant differences were observed in C_us in serum after i.v. and oral administration in AIDS patients compared with those in healthy volunteers despite higher C_{tot}s. Differ-

ences in serum protein binding may partially explain altered clindamycin pharmacokinetics in patients with AIDS. Further investigation is needed in order to more fully understand clindamycin disposition in AIDS patients, particularly in the presence of opportunistic infection.

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