Meal Composition Effects on the Oral Bioavailability of Indinavir in HIV-Infected Patients

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Purpose. To study the influence of large-volume high-calorie protein, fat, and carbohydrate meals and a non-caloric hydroxypropylmethyl cellulose (HPMC) viscous meal on the oral bioavailability of indinavir in HIV-infected subjects.

Methods. Seven male HIV-infected subjects received caloric meal treatments and control meals in a randomized crossover fashion and the viscosity meal as a final treatment. The total volume of each meal treatment was 500 mL and the caloric meals each contained 680 kcal. Gastric pH was also monitored by radiotelemetry from one hour before to four hours after drug and caloric meal administration. A single Crixivan™ (indinavir sulfate) dose equivalent to 600 mg indinavir was administrated orally with 100 mL of water immediately following meal administration. Indinavir plasma concentrations were obtained using reverse-phase HPLC.

Results. All meal treatments significantly decreased the extent of indinavir absorption as compared to fasted control. $AUC_{0-\infty}$ decreased by 68%, 45%, 34%, and 30% for protein, carbohydrate, fat, and viscosity meal treatments versus fasted control, respectively ($p < 0.05$). The mean C_{max} was significantly decreased 74%, 59%, 46% and 36% ($p < 0.05$) and the mean t_{max} was significantly delayed from 1 hr in fasted controls to 3.8, 3.6, 2.1 and 2.0 hrs ($p < 0.05$) for protein, carbohydrate, fat, and viscosity meal treatments, respectively. The elimination half-life of indinavir determined in the fasted state was decreased in HIV-infected subjects as compared to the reported half-life in normal healthy subjects.

Conclusions. Reductions in indinavir plasma concentrations compared to drug administration in the fasted state are most severe with the high-calorie protein meal. This is consistent with an influence of elevated gastric pH on drug precipitation. Significant drug plasma concentration reductions observed with administration of the other meals in the absence of appreciably elevated gastric pH profile indicate that other factors are playing a role in the meal effects. The similarity in indinavir plasma profiles with protein and carbohydrate versus fat and viscosity suggests that the latter meals may reduce the impact of drug precipitation compared to the former meals.

KEY WORDS: meal effect; food effect; indinavir; protease inhibitors; oral absorption.

INTRODUCTION

In a recent publication in *Pharmaceutical Research*, pharmacoscintigraphy was employed to examine meal effects on the bioavailability of the HIV-1 protease inhibitor, saquinavir (1). Drug plasma levels are increased as compared to oral administration in the fasted state when saquinavir is administered with a high-calorie, high-fat meal. Similar observations have been made with the HIV-1 protease inhibitor, nelfinavir (2). This increase is attributed to increased drug dissolution in the GI tract with meal administration. This information has been utilized in dosage formulation to improve the oral bioavailability of saquinavir and nelfinavir (3).

In contrast, the oral bioavailability of indinavir is decreased when the drug is taken with a high-calorie, high-fat meal in healthy human subjects (4). Indinavir, is a weak base with two titratable functional groups with pK_a 5.9 and 3.7 and a log octanol/water distribution coefficient of about 3 at pH 7.0. The drug is poorly water soluble at physiological pH (70 μg/mL) and very soluble (>1g/mL) in acidic solution. The high distribution coefficient suggests that intestinal absorption should not be limited by membrane permeation although a potential P-glycoprotein limitation to absorption has been reported (5). Consistent with the fact that low pH should enhance the dissolution rate, it has been shown that the oral bioavailability of indinavir can be significantly increased when the drug is administrated with 50 mM citric acid in dogs (6).

Given the high dose and low solubility at intestinal pH, dissolution rate would be expected to limit the drug's absorption. The drug is orally administered as the sulfate salt (Crixivan®) at high doses (typically 800 mg). Indinavir sulfate has higher water solubility at typical gastric pH than the other marketed HIV-1 protease inhibitors and might be projected to precipitate under meal conditions that mediate an elevation of gastric pH. In this regard, it has been shown that the negative meal effect on oral bioavailability can be minimized with light meals with high doses of indinavir in healthy subjects (4). The present study was initiated to determine the role of gastric pH in reducing oral indinavir bioavailability as a function of high-calorie meal composition in HIV-infected subjects. Based on findings of a negative meal effect on drug absorption in a recent Pharmaceutical Research report (7), the influence of meal viscosity on drug plasma levels was also investigated.

MATERIALS AND METHODS

Human Subjects

Seven male HIV-positive subjects were recruited from the HIV/AIDS program at the University of Michigan. The subjects were 41 ± 18 (mean ±SD) years old and included two African American and five Caucasian males of ±15% ideal body weight and with adequate baseline organ function. None of the subjects was taking either cytochrome P450 (CYP450)-inducing drugs or CYP4503A4-inhibiting agents for at least 14 days before the study and no alcohol was taken for at least 48 hours prior to the study. Subject clinical characteristics and their current drug therapy are included in Table 1. Subjects who were already taking indinavir received the study dose rather than their routine morning dose and resumed their standard therapy 8-hours later.

Materials

All meals tested in the meal composition studies are commercially available. These included protein (Promod®, Ross

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ABBREVIATIONS: HPMC, hydroxypropylmethyl cellulose; CYP4503A4, cytochrome P450 3A4; HC, Heidelberg capsule

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Table 1. Subject Characteristics

Subject #	1	2	3	4	5	6	7
CD4 count/μl	656	416	151	800	288	540	514
Plasma HIV RNA (copies/mL)	<400	2399	1869	<400	<400	<400	934
AIDS associated illnesses	—	bacterial pneumonia	bacterial endocarditis	—	—	PCP pneumonia	—
CDC stage	A2	B2	B3	A2	B3	C3	B1
Treatment							
Antiretroviral	zidovudine lamivudine indinavir	zidovudine lamivudine	stavudine didanosine lamivudine	zidovudine lamivudine	zidovudine didanosine	zidovudine lamivudine indinavir	
Prophylaxis	—	—	tmp/smx*	—	tmp/smx*	tmp/smx*	—

* tmp/smx = trimethoprim/sulfamethoxazole.

Labs), carbohydrate (Moducal®, Mead Johnson), fat (Microlipid®, Sherwood Medical), and HPMC (Methocel®, Dow) meals. Indinavir sulfate (Crixivan®, Merck & Co.) capsules, each containing 200 mg equivalent of free base indinavir, were obtained from the University of Michigan hospital pharmacy. Indinavir (L-735,524) and its internal HPLC standard (L-738,804) were generously supplied by Merck & Co.

Study Design and Procedures

The study protocol was approved by the Internal Review Board at the University of Michigan Medical School. All the studies were performed at the Clinical Research Center at the University of Michigan Hospital. Written consent was obtained from the subjects before their enrollment in the study. Subjects were fasted overnight prior to the study and until 4 hours after drug administration. In each treatment phase, indinavir sulfate (Crixivan®, Merck & Co.) was administered as a single oral dose of 600 mg (three 200 mg capsules) at 8:00 am with 100 mL water. In the control phase, 500 mL of water was consumed (with no meal content) prior to administration of indinavir. Each meal treatment utilized a total volume of administration of 500 mL. The lipid, protein and carbohydrate meals each contained 680 kcal as low viscosity liquid meals. Two percent (w/v) of aqueous hydroxypropylmethylcellulose (HPMC, mixture of Methocel® K15M and K4M) with a viscosity of 10,000 cp was administered to assess non-caloric meal viscosity effects. This viscosity is equivalent to that of a mixed-calorie solid meal homogenate (7). Each meal was consumed over a 15-minute period immediately prior to drug administration. While the control and calorie meal treatments were studied in the seven subjects in a four-way crossover design, the viscosity meal was added on as a final study in each patient. Blood samples were obtained prior to drug administration and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6 and 8 hours after drug administration. A standard lunch was provided 4 hours after drug administration and GI pH was monitored from 60 minutes prior to test meal and drug administration until lunch. Blood was centrifuged and resultant plasma samples were kept frozen at −70°C until analysis.

Gastric pH Measurements

A Telefunken Heidelberg capsule (Heidelberg International, Inc., Blairsville, GA) was employed for continuous monitoring of gastric pH for one hour prior to and 4 hours following drug and meal treatment administration. These measurements were obtained only in the four-way crossover study and not with the viscosity meal phase of the study. The Heidelberg capsule is a small, non-digestible, radiotelemetry unit that measures hydrogen ion concentration in the GI tract and converts this to a radio signal transmitted to an antenna worn in a belt by the subjects. The Heidelberg capsule was activated in water and calibrated in buffers at pH 1 and pH 7 and a thin string was attached to the capsule. The subjects swallowed the Heidelberg capsule with 100 mL of water and the string was taped to the subject at a length consistent with maintaining its position in the stomach.

Drug Analysis

Plasma concentrations of indinavir were determined utilizing a modified reverse-phase HPLC method and plasma analysis was performed with appropriate biohazard controls (8,9). A Waters HPLC system was used, which included a Waters 510 Pump, WISP 710B Auto-sampler, 486 Tunable Absorbance Detector, and 746 Data Module. The chromatographic conditions included a Hypersil BDS C8 (Alltech, IL) column, a 40% acetonitrile/15 mM phosphoric acid mobile phase, with pH adjusted to 6.0 with triethylamine, a flow rate of 1.0 mL/min and a detection wavelength set at 210 nm.

Plasma samples of indinavir were extracted before HPLC injection in the following manner. Briefly, a 0.5 mL plasma aliquot was combined with 500 ng of internal standard and alkalinized with 0.1 mL 1N NaOH. Then 5 mL of diethyl ether was added and after vortexing the sample for 2 minutes, the mixture was allowed to stand for 5 minutes to achieve phase separation. The organic layer was then transferred to a clean tube and evaporated to dryness under nitrogen. The residue was reconstituted in 250 μL of mobile phase, and 200 μL was injected onto a Hypersil BDS C8 analytical column (Alltech, Ill.). The mobile phase consisted of acetonitrile/phosphoric acid (15 mM) [40:60, vol/vol] adjusted to pH 6.0 with triethylamine) at a flow rate of 1.0 mL/minute with uv detection at 210 nm. The lower limit of detection for this assay was 100 ng/mL.

The concentration of indinavir in each plasma sample was calculated by unweighted least-squares regression of the peak area ratio (protease inhibitor/internal standard) of spiked plasma standards versus concentrations. The accuracy and precision of the assay are summarized in Table 2.

Table 2. Indinavir HPLC Assay Validation

Nominal Indinavir concentration (μg/mL)	Accuracy (%)	Precision inter-day (%)	Precision intra-day (%)
0.1	109.2	7.01	8.6
0.25	100.3	11.5	0.9
0.5	93.0	4.7	3.8
1.0	92.3	10.2	1.5
5.0	100.0	3.4	3.1
10.0	100.4	2.0	1.5

Data Analysis

Indinavir plasma-concentration time data were individually graphed and analyzed by noncompartmental methods. The maximum indinavir plasma concentration (C_{max}) and time to maximum plasma concentration (t_{max}) were obtained by visual inspection of the profiles. The area under the concentration-time curve (AUC_{0-8hr}) was calculated using trapezoidal and log trapezoidal rules. The $AUC_{8hr-\infty}$ was calculated using C_{8hr} divided by k_e, where k_e is elimination constant obtained from nonlinear regression of the terminal data points. Elimination half-life in the fasted state ($t_{1/2}$) was calculated as (ln 2)/k_e. Control and meal treatment pharmacokinetic parameters were compared by one-way repeated-measures analysis followed by a Donnet's pair-wise comparison. A P-value of 0.05 was considered significant.

RESULTS

Each of the seven subjects enrolled in the study completed all five phases of the study, with the exception of subject number one, who was unable to complete the viscosity phase of the study due to loss of venous access after removal of a broviac catheter.

Gastric pH

Figure 1 illustrates the mean gastric pH during baseline monitoring and following consumption of study meal over the five-hour monitoring period. Individual patient profiles all followed mean data trends. Co-administration of indinavir with the large volume of water in the control phase resulted in essentially no change in gastric pH. After consumption of fat and carbohydrate meals, the pH for each subject was elevated less than 1 unit and returned back to baseline in less than 5 minutes and 30 minutes, respectively. In contrast, co-administration of indinavir with protein meals resulted in elevated gastric pH that persisted throughout the monitoring period. None of the subjects showed a baseline gastric pH that was elevated in the pre-administration monitoring period indicative of compromised acid secretion.

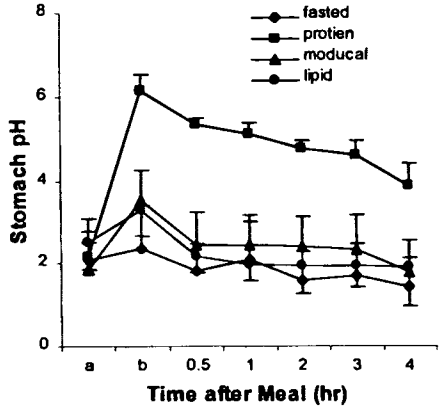

Fig. 1. Stomach pH changes after meal administration. (a) Stomach pH before meal. (b) Stomach pH immediately after meal.

Meal Effects on the Pharmacokinetics of Indinavir

The mean indinavir plasma concentration-time profiles following oral administration in the fasted state and protein, lipid, carbohydrate or HPMC meals are shown in Fig. 2. Table 3 provides the mean indinavir $AUC_{0-\infty}$, C_{max} and t_{max} for the seven subjects during each of the five meal treatment phases. The $AUC_{0-\infty}$ of indinavir was significantly decreased ($p < 0.05$, Donnet's pair-wise comparison method) by 68%, 45%, 33% and 30% during protein, carbohydrate, fat and viscosity meal phases, respectively. The mean C_{max} was significantly decreased and the mean t_{max} significantly increased during each of the meal phases compared to fasted controls. The protein meal also significantly decreased indinavir $AUC_{0-\infty}$ compared to each of the other meal treatments. The mean elimination half-life of indinavir determined in the fasted state control study was 0.98 ± 0.23 hrs (mean ± SD).

Individual plasma profiles are given in Fig. 3. On an individual basis, the effect of protein on AUC, C_{max} and t_{max} was consistent in all seven subjects. In one subject (#7), drug plasma concentrations with the non-calorie viscosity meal were not different from control administration with water, while all three high-calorie meals greatly decreased drug plasma concentrations. In one subject (#1), administration of a carbohydrate

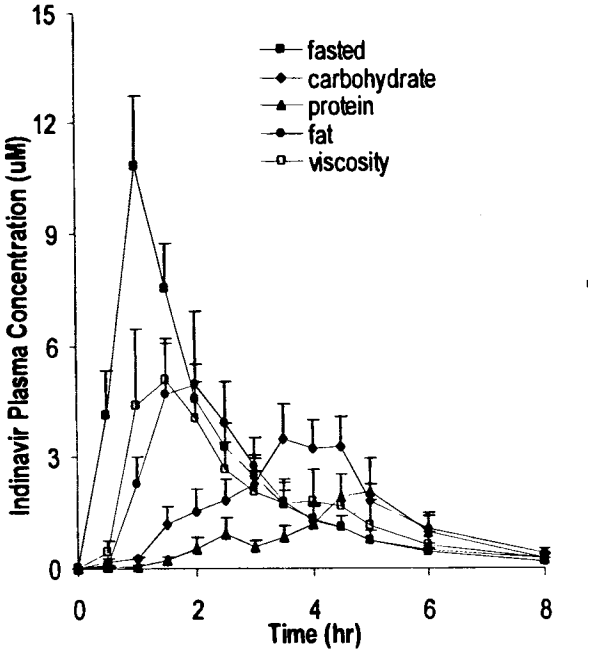

Fig. 2. Indinavir mean plasma levels after fasted-state administration and co-administration of different liquid composition meals (mean + SEM).

Table 3. Summary of Indinavir Pharmacokinetics Following Single Doses of 600 mg of Indinavir with Fasted Control and Co-Administration of Different Meal Compositions

Treatment	AUC_{0-inf} (μM·hr)[a]	AUC ratio (%)	C_{max} (μM)	C_{max} ratio (%)	T_{max} (hr)
Fasted	20.10 ± 7.22	100.00 ± 35.90	12.01 ± 4.08	100.00 ± 33.98	1.08 ± 0.19
Protein	6.40 ± 5.59*	31.83 ± 27.81	2.89 ± 2.12*	25.78 ± 11.69	3.83 ± 1.04*
Carbohydrate	11.06 ± 6.61*,**	55.00 ± 32.89	4.62 ± 2.33*,**	41.22 ± 19.44	3.58 ± 0.89*
Fat	13.56 ± 8.96*,**	67.45 ± 44.54	6.08 ± 4.56*,**	54.20 ± 37.98	2.08 ± 0.53*
HPMC	14.05 ± 6.00*,**	69.86 ± 29.83	7.15 ± 3.62*,**	63.78 ± 30.10	2.00 ± 1.30*

[a] Data were mean ± SD (n = 7).
* Significant difference from fasted control ($p < 0.05$, Donnet's pair-wised comparison).
** Significant difference from protein meal treatment ($p < 0.05$, Donnet's pair-wised comparison).

meal did not decrease drug plasma levels to the same extent as the other three meals. In fact, if this subject's carbohydrate data is not included in analysis, the mean indinavir plasma profiles with protein and carbohydrate meals are very similar (data not shown). Fat meals caused large decreases in drug AUC in three (#1, #4, and #7) subjects but only small decreases in the other four subjects. In this regard, the fat meals provided the greatest variability in drug plasma profiles among the various meal treatments.

DISCUSSION

The weak base, indinavir, with pK_as at 3.7 and 5.9, is highly water soluble at gastric pH. However, it might be expected that the drug would precipitate at high pH to limit its availability for absorption in the gastrointestinal tract. This projection is consistent with indinavir's pH-solubility profile (700 μg/mL at pH 5.2 and 70 μg/mL at pH 7.4) (10) and the drug concentration (600 mg/500 mL or 1.2 mg/mL) administered in this study.

Elevation of gastric pH from meal intake could depress the dissolution rate of indinavir as well as increase the potential for dissolved drug to precipitate. In the subjects in this study, elevation of gastric pH was observed to be a strong function of meal composition. Basal gastric secretion appeared to be normal in these subjects as the gastric pH rapidly returned to baseline after co-administration of indinavir with a lipid or carbohydrate meal. Consistent with the high buffer capacity of the protein meal, gastric pH remained elevated during the 4-hour monitoring period in all of the subjects. Furthermore, co-administration of indinavir with the protein meal provided the greatest and most consistent negative meal effect as drug plasma levels showed the greatest decrease compared to controls in all of the subjects. This is compatible with the hypothesis, that elevation of gastric pH by the protein meal promoted indinavir precipitation and decreased its availability in solution for intestinal absorption. However, negative meal effects on mean indinavir plasma levels were also observed with the fat and carbohydrate meals in spite of the fact that they did not significantly alter gastric pH in these subjects.

Given the limited effect of the carbohydrate meal on gastric pH, the significant decrease in indinavir plasma concentrations might be regarded as surprising in contrast with the protein meal. Since a similar slowing of gastric emptying is expected from the equivalent caloric density administered for protein and carbohydrate meals versus controls, the similarity in mean indinavir t_{max} from these two meals might be projected to be a function of similar meal effects on gastric emptying. However the earlier mean t_{max} with the fat meal, which should equivalently slow gastric emptying, may indicate that the similarity in effect of carbohydrate and protein is through an indinavir precipitation effect which is not as effectively promoted by the fat meal. Carbohydrate-stimulated water absorption might serve to reduce the fluid volume available for drug dissolution in the upper GI tract and promote drug precipitation to a greater extent then would be the case with the fat meal. This might account for the similarity in indinavir plasma level profiles with protein and carbohydrate meals that may promote precipitation of indinavir through different mechanisms.

For drugs with poor solubility and slow dissolution rate in the small intestine, fat meals typically enhance drug absorption by increasing intestinal fluid volume through stimulation of pancreatic secretions and promotion of drug solubilization via biliary secretion (11). This appears to be the case for other HIV-protease inhibitors like saquinavir (1) and nelfinavir (2). In this study, the fat meal caused a negative effect on indinavir absorption. This apparent difference in drug solubilization with lipid meals may be a function of dissolution rate of the commercial protease inhibitor products. Rapid dissolution of indinavir sulfate may provide a greater potential for precipitation than for saquinavir and nelfinavir. Slower dissolution of saquinavir and nelfinavir might be increased by lipid solubilization. In addition, the possibility of a fat-stimulated bile acid effect to reduce the absorption of indinavir cannot be excluded. The absorption of some weakly basic drugs may be decreased with bile secretion through formation of a drug-bile acid complex (12).

Dietary fiber is known to alter the motility of the stomach and small intestine and slow gastric emptying (13). Increasing the viscosity of the lumenal contents may also impair drug transport to absorbing membranes in the upper intestine for absorption (7). In this study in HIV subjects, a non-caloric viscous meal was employed to mimic the upper intestinal viscosity typical of high-fat, solid meal homogenates. In a previous study in dogs, meal viscosity was demonstrated to be sufficient to mimic a negative meal effect on the plasma levels of an orally administered high-pK_a, weak base antiarrhythmic drug (7). This canine viscosity study was motivated by the fact that this drug was preferentially absorbed in the upper small intestine and the observation that liquid meals only delayed drug absorption while equivalent-calorie solid meals and solid meal homogenates also greatly reduced the drug's oral bioavailability.

The early t_{max} (0.8 h) reported for indinavir (4) suggested that a meal viscosity effect on upper intestinal absorption might

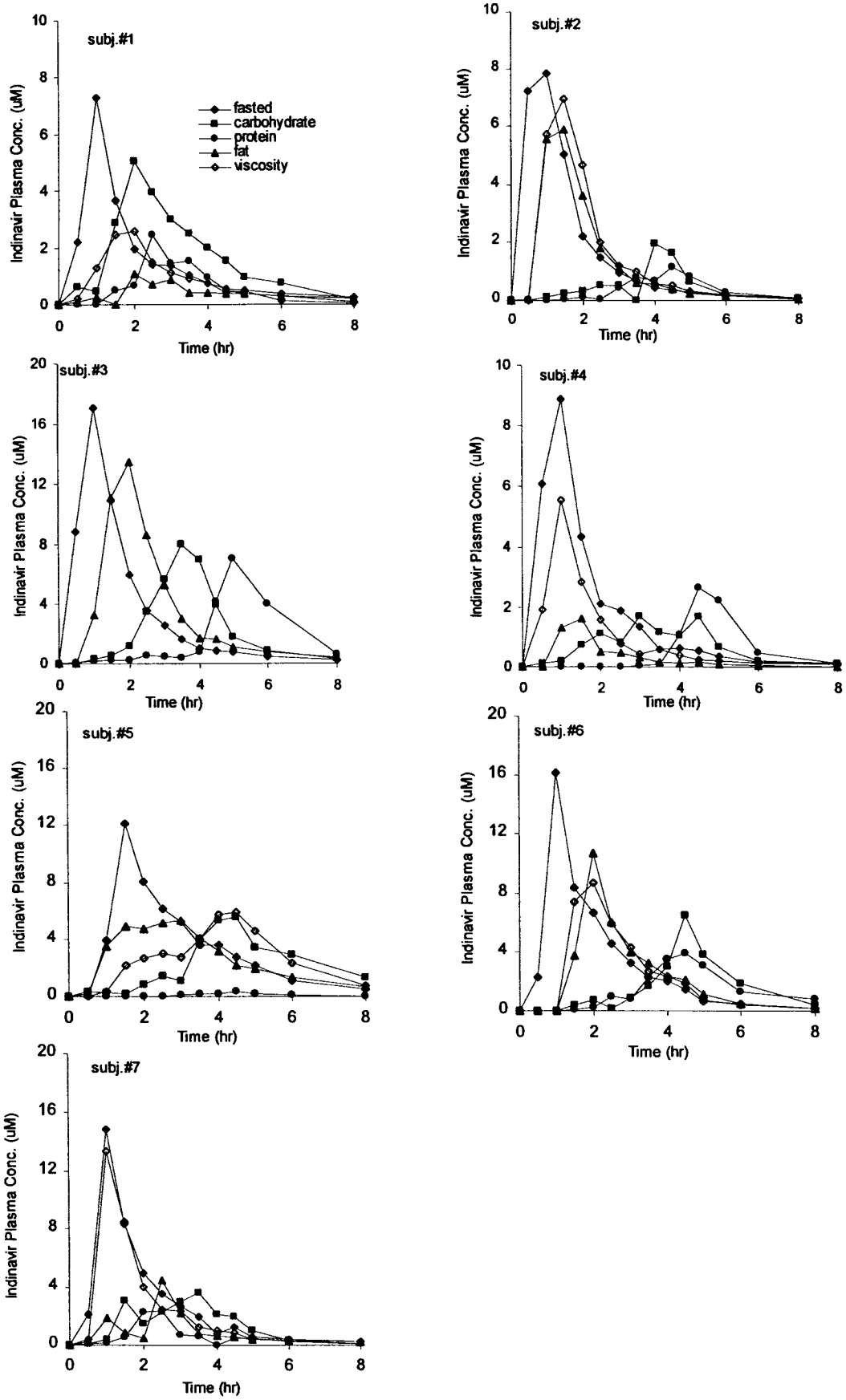

Fig. 3. Indinavir plasma levels after fasted-state administration and co-administration of different liquid composition meals.

play a role in the negative meal effect. In this study in HIV-infected subjects, the same HPMC meal utilized in the canine study was sufficient to produce a decrease in indinavir plasma concentrations as compared to fasted state administration of an equivalent volume of water. However, as compared to the protein meal, it is apparent that viscosity or drug sequestration by the HPMC meal is not sufficient to account for the negative meal effects previously reported for indinavir with high calorie meals. Furthermore, both high-calorie solid and liquid meals decrease indinavir plasma levels to the same extent. It is of interest, however, that the decreased indinavir bioavailability and delayed t_{max} with the viscous non-caloric meal were similar to that observed for the fat meal as compared to those observed for carbohydrate and protein meals. This may indicate that the lipid and HPMC meals do not promote upper GI precipitation of indinavir to the same extent as the carbohydrate and protein meals. Lipid sequestration of indinavir and viscosity effects on diffusion may serve to depress drug nucleation steps toward precipitation as compared to protein and carbohydrate meals.

In a previous study, it was reported that systemic availability of indinavir was 4.9 times higher from a 1000 mg oral dose than from a 400 mg oral dose in healthy subjects (4). This greater-than-proportional increase argues against a solubility effect and for a saturation of first pass elimination effect controlling plasma levels from oral administration. This is also supported by the fact that negative meal effects on indinavir plasma levels are not observed when given with ritonavir (an inhibitor of cytochrome P4503A metabolism) in HIV-infected patients (14). Roughly equivalent biotransformation K_m in human enterocyte and hepatocyte microsomes (15) are two orders of magnitude below minimal concentrations of indinavir in the intestinal lumen (115 μM at pH 7.4) suggesting that metabolism is always saturated in intestinal epithelia and that portal blood concentrations may saturate hepatic metabolism. However, meal effects on indinavir dissolution-rate and precipitation in the GI tract might be expected to influence the rate of indinavir absorption and amplify the impact of first-pass elimination on indinavir plasma levels. It has been reported that more than 83% of an orally administered indinavir dose is excreted in human feces of which less than 20% was parent drug (16). This suggests a role for biliary secretion of hepatic metabolite with a possible secretory contribution of intestinal metabolite. Higher indinavir concentrations in the intestine versus portal blood and the fact that 57% of an intravenous 10 mg/kg indinavir dose is excreted in the bile of rats (16) may suggest a greater role for hepatic first-pass elimination. Both the high caloric and viscous test meals delay gastric emptying, which may reduce indinavir-input rate from the stomach to small intestine. Differences in the impact of protein and carbohydrate meals versus lipid and viscous meals may reflect differences in drug precipitation on absorption rate (as reflected by t_{max}) controlling the extent of first-pass elimination on indinavir plasma levels.

The present study shows that the absorption of indinavir was rapid in HIV-infected subjects in the fasting state with a t_{max} of 1.1 ± 0.2 hours (mean ± SD) similar to previous observations (4) in healthy subjects (t_{max} = 0.8 h). However, the elimination half-life of indinavir is decreased to 0.98 ± 0.23 hr in HIV-infected subjects as compared to reported values of 1.8 ± 0.4 hr in healthy subjects (4). In another indinavir absorption study in HIV-infected subjects receiving an 800 mg oral dose, it was shown that three out of four subjects showed shorter indinavir elimination half-lives than observed in healthy subjects (8). The shorter half-life might further decrease the bioavailability of indinavir in HIV-infected patients. Furthermore, systemic concentrations of short half-life drugs are more sensitive to absorption variability. The shorter elimination half-life in HIV-infected subjects may be a function of drug therapy and/or disease.

Administration of single doses of indinavir (200 and 400 mg) to healthy subjects with a high-fat mixed composition breakfast of 784 kcal in a total volume estimated between 400–500 mL decreased AUC 60–80% and C_{max} by 70% compared to fasted administration with 250 mL of water (4). This meal increased indinavir t_{max} from 0.7 to 2h for the 400mg dose and from 0.9 to 2.8h for the 200mg dose. In this same study neither elimination half life nor protein binding was seen to be dose dependent. In the present study in HIV-infected patients, a similar percent decrease in AUC and C_{max} are observed with the 680 kcal, 500 mL protein meal. Given the differences in indinavir elimination half-life between healthy and HIV-infected subjects, the similarity in the magnitude of the meal effect is likely related to absorption rate effects on first-pass elimination.

In conclusion, the primary aim of this work was to compare the oral bioavailability of indinavir with high-volume, high-calorie meals of different compositions. It was expected that the protein meal would elevate gastric pH and decrease indinavir absorption and this was observed in all patients. The negative effect of the carbohydrate meal in most patients was not anticipated and the promotion of water absorption is hypothesized to mediate indinavir precipitation. The fat meal provided the greatest intra-subject variability with respect to decreasing drug plasma concentrations. The viscosity meal was an added treatment based on a recent canine study in which solid but not liquid meals reduced the extent of drug absorption (7). The smaller decreases in indinavir plasma concentrations observed with the fat and viscosity meals may be the result of a reduced potential for drug precipitation as compared to the other meal treatments. Meal effects on reducing lumenal drug concentrations in the small intestine may serve to alter the rate of absorption to elevate the extent of first-pass metabolism and reduce indinavir bioavailability.

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