Methods for Integration of Pharmacokinetic and Phenotypic Information in the Treatment of Infection with Human Immunodeficiency Virus

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Interest in monitoring antiretroviral drug concentrations in human immunodeficiency virus–infected patients has gained considerable momentum in recent years. We present a potential method for integrating pharmacokinetic and phenotypic information that will assist clinicians in choosing optimal treatment regimens for their patients and that will provide an approach for the interpretation of antiretroviral plasma drug concentrations.

A considerable amount of interest has been generated regarding the importance of plasma concentrations of antiretroviral drugs, especially HIV protease inhibitors (PIs), and the role that inadequate drug concentrations may play in treatment failure or drug resistance [1]. Dose-response relationships exist for PI monotherapy and combination therapy for HIV infection, in which higher doses of the drug are associated with a more durable suppression of plasma HIV RNA. Underlying concentration-response relationships also exist in which lower drug concentrations are associated with less durable responses and development of genotypic mutations and drug resistance. For many of the antiretroviral drugs, such concentration-response relationships have been observed. Failure to maintain adequate concentrations will eventually allow drug-resistant virus isolates to become the predominant population, thereby decreasing the probability of response to current and subsequent therapies. PIs, when administered alone or with nucleoside analogs, produce average trough concentrations (C_{min}) very close to the in vitro IC_{50} or IC_{95} (the concentrations required to inhibit 50% or 95% of viral replication in vitro, respectively), after adjusting for protein binding. Consequently, poor adherence to therapy, altered absorption or disposition, and a large degree of between-patient pharmacokinetic variability may result in low drug exposure. Exposure of replicating virus to suboptimal drug concentrations will eventually lead to the selection of drug-resistant isolates. An improved understanding of these pharmacodynamic relationships has led to the use of combination PI regimens that take advantage of favorable drug interactions, produce appreciably elevated plasma concentrations, and allow for more-simplified dosing regimens.

Antiretroviral pharmacodynamics have also led to the evaluation of therapeutic drug monitoring of the PIs and nonnucleoside reverse-transcriptase inhibitors. Of the many caveats to consider when implementing therapeutic drug monitoring, uniform interpretation of plasma drug concentrations is probably the most significant. When incorporating pharmacokinetic information into the choice of a particular PI-based salvage regimen, the overriding concern is the probability of an individual patient achieving and maintaining trough concentrations greater than the susceptibility of their virus isolate or isolates. The objectives of this article were (1) to consolidate important antiretroviral pharmacokinetic information from the literature into a single source, (2) to develop a practical approach to aid clinicians in the interpretation of antiretroviral plasma drug concentrations, and (3) to provide a mechanism to help facilitate the selection of optimal drug regimens when used in conjunction with phenotypic information for salvage therapy.

Materials and methods. Pharmacokinetic information on the various antiretroviral treatment regimens was obtained from the literature, including full-length articles and abstracts. One- or 2-compartment pharmacokinetic models were then developed for each regimen. The 1-compartment model parameters were oral clearance (CL/F), terminal distribution volume (V_z/F), absorption rate constant (k_a), and absorption lag phase (t_{lag}). Two-compartment parameters included total (CL_t/F) and distributional (CL_d) clearance, central (V_c/F) and peripheral (V_p/F) distribution volumes, and k_a and t_{lag}. To account for intersubject pharmacokinetic variability, all clearance and distribution volumes were assigned a coefficient of variation (CV) of 40%. A CV of 50% was applied to k_a and t_{lag}. Several of the references provided SDs, but we chose to use fixed values that accurately represent the true variability across all regimens

Received 6 August 2002; accepted 21 October 2002; electronically published 14 January 2003.

Financial support: Adult and Pediatric AIDS Clinical Trials Group, National Institute of Allergy and Infectious Diseases (grants U01-AI38858 and U01-AI41089).

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Clinical Infectious Diseases 2003;36:373–7

1058-4838/2003/3603-0021$15.00

studied. A linear SD variance model was used to describe additional assay variability.

All models were implemented by the Adapt II software package, release 4 (Biomedical Simulations Resource) [2]. One hundred Monte Carlo population simulations with output error and lognormal parameter distribution were performed for each regimen. The steady-state concentration-time points were 0, 1, 2, 3, 4, 5, 6, 8, 10, and 12 h after dose administration for twice-daily regimens; additional points at times 16, 20, and 24 h after dose administration were added for once-daily regimens. These concentration-time data were used to produce the tenth, 25th, 50th (median), 75th, and 90th percentile curves for each dosing regimen.

Results. The simulated concentration-time curves generated from the 1- and 2-compartment models are shown in figure 1. Pharmacokinetic parameters for each regimen are listed in table 1. All parameters listed in table 1 are within 20% of the corresponding literature values. The amprenavir/ritonavir regimens were best described by a 2-compartment model; a 1-compartment model was used for the remaining regimens. Overall, the pharmacokinetic models were able to adequately describe the resulting concentration-time curves for each regimen evaluated.

Discussion. We describe a potential method to aid clinicians in the interpretation of antiretroviral plasma drug concentrations and provide an additional tool to help facilitate the selection of optimal drug regimens when used in conjunction with virus susceptibility information for salvage therapy. One- or 2-compartment models were used to describe the concentration-time curves for various antiretroviral regimens. Modeled results are in close agreement with pharmacokinetic data published elsewhere (table 1). Clearly, the simulated results will be only as accurate as the study from which the original parameters were derived. These results indicate some discrepancies between the 2 indinavir/ritonavir regimens. Although pharmacokinetic data from healthy volunteers are available for these regimens [15], they were not used, because the influence of HIV infection on antiretroviral pharmacokinetics is currently unknown.

Results from these simulation studies serve several important purposes. The first is consolidation of essential pharmacokinetic data from the literature into a single source. The second purpose is to aid in the interpretation of antiretroviral plasma drug concentrations. Each plot depicted in figure 1 shows the median concentration-time curve and the variability around that curve. Therefore, if a plasma sample was obtained from an individual patient for determination of drug concentration, these figures will allow the clinician or other health care professional to determine how that patient's data compare with data from the population. For example, if a nelfinavir concentration (measured 10 h after receipt of a dose) was determined to be 0.4 mg/L, this would indicate that (1) this patient has a high CL/F, (2) the patient has low bioavailability (i.e., the drug had not been taken with an appropriate high-fat meal), or (3) the patient does not adhere to the regimen. Clearly, it is not in the best interest of the patient to implement a regimen change solely on the basis of 1 drug level. However, if >1 level demonstrates a consistent pattern, options would include (1) counseling the patient on adherence to therapy and proper administration of the agents, (2) increasing the dosage to 1500 mg b.i.d., or (3) changing the regimen. The last and probably the most important purpose is to provide an additional tool for optimization of salvage therapy when used in conjunction with phenotypic data.

A phenotypic test provides a direct link between drug exposure and virus susceptibility; therefore, combining this information when choosing a salvage regimen has considerable merit. A patient that has cycled through several PI-containing regimens likely has genotypic mutations and reduced virus susceptibility. This would be reflected in a phenotypic test as a fold change in susceptibility and an increased IC_{50}. For example, a phenotypic report for an individual patient states that amprenavir, indinavir, and lopinavir are 11-fold, 20-fold, and 37-fold resistant, respectively. The corresponding IC_{50}s of these drugs are 0.204, 0.138, and 0.183 μM, respectively. Solely on the basis of the fold changes, it is reasonable to assume that amprenavir (administered with low-dose ritonavir) may be the most appropriate option in terms of PI-based therapy for this patient. The concentration-time curves provided in figure 1 suggest that additional options are available. When corrected for protein binding and converted to the units of mg/L, the IC_{50}s of amprenavir, indinavir, and lopinavir are approximately 1.03, 0.212, and 5.75 mg/L, respectively.

A discussion on protein-binding correction and a table listing the conversion factors for various antiretrovirals (from μM to mg/L) was recently published [16]. Because phenotypic tests currently do not take into consideration the extent of drug-protein binding, a simple way to account for this is to divide the IC_{50} by the free fraction of drug. This technique is not exact, but it provides results close to the range expected on the basis of in vitro protein-binding experiments [17, 18]. According to figure 1, the trough concentration of amprenavir of 1.03 mg/L is achievable with amprenavir/ritonavir administered at a dosage of 600/100 mg b.i.d. Because the corrected IC_{50} falls around the 25th percentile of the population average concentration-time curve, this patient would have a 75% probability of achieving plasma concentrations greater than their individual IC_{50}. Similarly, the corrected IC_{50} of indinavir falls around the tenth percentile curve, indicating that the indinavir/ritonavir regimens also have a high probability of achieving adequate plasma concentrations. The lopinavir-corrected IC_{50} is approximately at the median (50th percentile) population concentra-

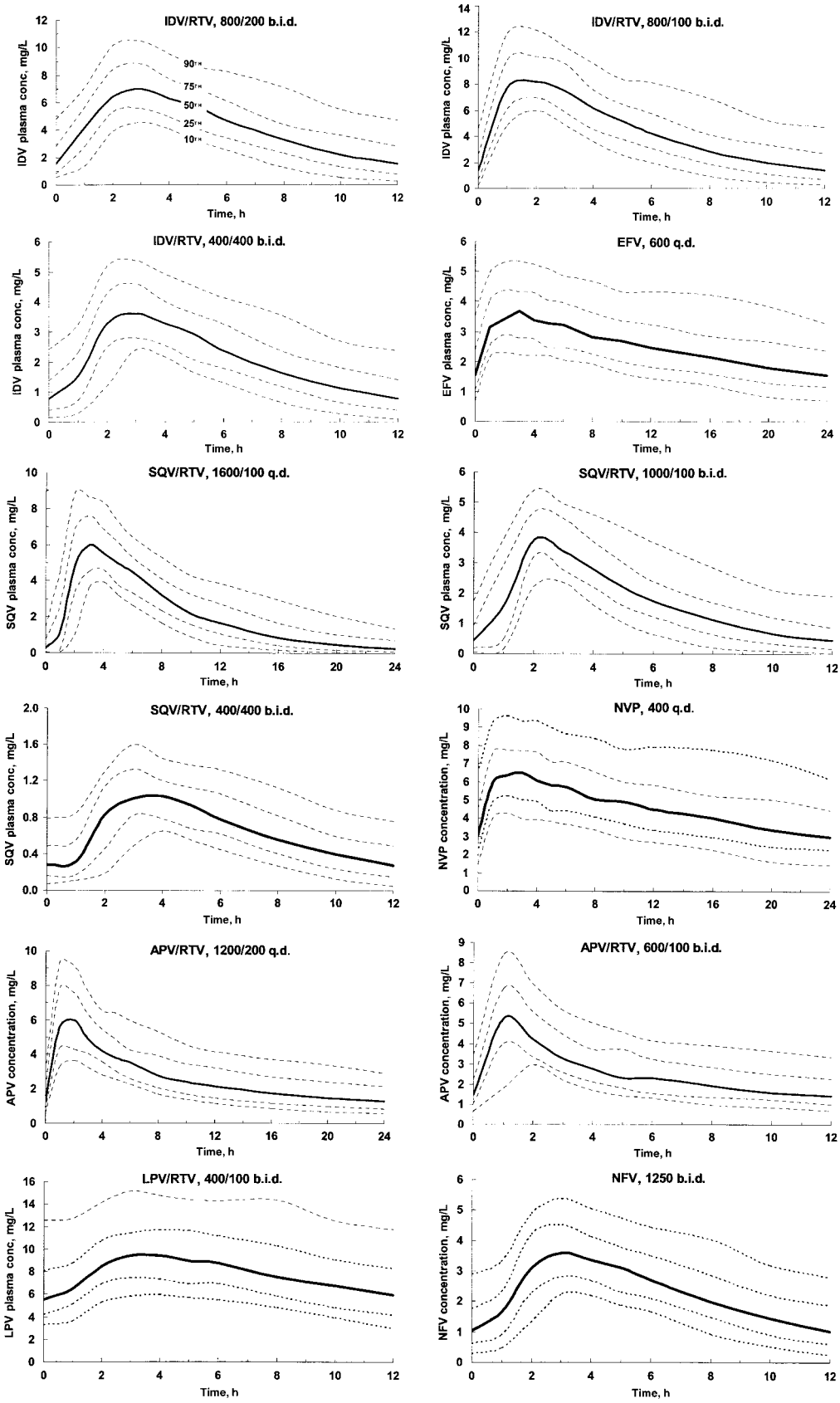

Figure 1. Simulated concentration-time curves for common regimens of protease inhibitor (PI), ritonavir-enhanced PI, and nonnucleoside reverse-transcriptase inhibitor therapy. Curves were generated with use of previously published pharmacokinetic data. The figure depicts the tenth, 25th, 50th (median [*solid line*]), 75th, and 90th percentile concentration-time curves for each regimen. APV, amprenavir; EFV, efavirenz; IDV, indinavir; LPV, lopinavir; NFV, nelfinavir; NVP, nevirapine; plasma conc, plasma concentration; RTV, ritonavir; SQV, saquinavir.

Table 1. Pharmacokinetic parameters of various antiretroviral agents and the simulated results.

	Literature values[a]				Simulated values[b]				
Treatment regimen	AUC_τ	C_{max}	T_{max}	C_{min}	AUC_τ	C_{max}	T_{max}	C_{min}	Reference
IDV/RTV									
800/200 b.i.d.	47.50	7.69	2.79	1.20	46.89	6.76	2.60	1.28	[3]
800/100 b.i.d.	46.60	8.90	1.40	1.30	50.06	8.25	1.60	1.16	[4]
400/400 b.i.d.	23.00	3.79	3.18	0.70	23.45	3.58	2.90	0.64	[3]
SQV/RTV									
1600/100 q.d.	48.15	6.98	3.50	0.17	49.14	6.13	3.00	0.19	[5]
1000/100 b.i.d.	18.84	3.66	2.00	0.40	19.15	3.77	2.00	0.47	[6]
400/400 b.i.d.	6.99	1.28	3.00	0.23	7.12	1.05	3.34	0.24	[6]
APV/RTV									
1200/200 q.d.	68.20	7.75	1.00	1.40	61.00	6.39	1.01	1.17	[7]
600/100 b.i.d.	29.88	6.01	0.95	1.71	29.21	6.25	0.87	1.37	[8]
LPV/RTV, 400/100 b.i.d.	83.96	9.30	4.20	5.96	88.67	8.78	3.98	5.35	[9–11]
NFV, 1250 b.i.d.	27.90	3.15	3.35	0.85	25.49	3.43	3.16	0.90	[12, 13]
EFV, 600 q.d.	54.80	3.63	2.00	1.55	56.66	3.26	2.36	1.45	[14]
NVP, 400 q.d.	101.80	6.69	1.50	2.88	104.60	5.85	1.80	2.84	[14]

NOTE. APV, amprenavir; AUC_τ, area under the concentration-time curve; C_{max}, maximum concentration; C_{min} trough concentration; EFV, efavirenz; IDV, indinavir; LPV, lopinavir; NFV, nelfinavir; NVP, nevirapine; RTV, ritonavir; SQV, saquinavir; T_{max}, time to maximum concentration.

[a] Data are mean or median values, depending on which were reported.

[b] Data are mean values.

tion-time curve, indicating that this regimen also has a reasonable probability of producing the desired concentrations, albeit slightly lower than the other 2 regimens. Evidence is accumulating that achieving appropriate concentrations in the presence of drug resistance will produce a more durable treatment response [19]. It is important to emphasize that choosing therapy on the basis of this approach does not ensure an adequate viral response but rather increases the probability that the desired response will occur. This approach allows the clinician and patient more options to choose from when considering salvage therapy regimens than may otherwise be available when a phenotypic test alone is used.

In summary, we present a practical method to aid in the interpretation of antiretroviral drug concentrations and provide an additional mechanism to facilitate the integration of data on pharmacokinetics and virus susceptibility when choosing salvage therapy regimens. Dose-response and concentration-response relationships have been identified. Higher plasma PI concentrations are associated with a more durable virus load suppression, which would be expected to confer a lower probability of the emergence of drug-resistant virus. As the incidence of drug resistance increases, drug sequencing and selection of salvage regimens will continue to play an important role in patient treatment.

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