A Pilot Study of Nelfinavir Therapeutic Drug Monitoring in HIV Infected Patients

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Introduction

- The goal of therapeutic drug monitoring (TDM) is to achieve plasma drug concentrations that fall within an acceptable therapeutic range, in order to maximize pharmacologic efficacy and minimize drug toxicity.
- In general, TDM is indicated in situations where the following conditions exist:
  - *drug:* good relationship exists between drug exposure and pharmacological response; drug has narrow therapeutic index
  - *patient:* wide interpatient variation exists in drug disposition, adherence is a challenge, other conditions (e.g., hepatitis, diarrhea) that can affect drug absorption or metabolism
  - *regimen:* potential for many complex drug-drug or drug-food interactions, that can significantly affect plasma drug concentrations
  - *disease:* treating a condition where significant morbidity/mortality is associated with drug failure
- While TDM is routinely used in other disease states, it is currently not routinely used in the management of HIV disease.

Protease Inhibitors as Candidates for Therapeutic Drug Monitoring

- Presently, there is a great deal of interest in TDM in the area of HIV. Protease inhibitors (PIs) are considered to be good candidates for TDM for a number of reasons:
  - PI are given at standard doses, but concentrations are often variable due to factors such as inter-patient variability (up to 10-fold at equal doses), complex drug interactions (mega-HAART), concomitant diseases (malabsorption, hepatic dysfunction), and non-adherence.
  - Variable drug concentrations are a concern, since PIs have a very short plasma half-life, and the ratio between achievable Cmins and minimum effective concentration is not very wide.
  - Preliminary data suggest that PI exposure correlates with virologic efficacy and drug toxicity; in the VIRADAPT study of patients on salvage therapy, having optimal PI levels (>IC50) was an independent predictor of viral load response at 48 weeks (OR 2.48).
- At present, the role of TDM in HIV has not yet been conclusively demonstrated, due to limitations in study design, heterogenous patient populations, and use of different PK parameters with non-standardized therapeutic ranges.
- Prospective data are lacking on the clinical utility of therapeutic drug monitoring (TDM) of protease inhibitors (PI).

Objective

- The purpose of this pilot study was to determine the potential value of nelfinavir (NFV) TDM in an ambulatory HIV clinic population.

Methods

- Over a 7 week period (March-May 1999), we randomly recruited ambulatory patients at the Toronto General Hospital Immunodeficiency Clinic who were taking nelfinavir 1250 mg BID as part of their antiretroviral regimen.
- Trough and/or peak samples were obtained and nelfinavir (and its metabolite) were measured; parent nelfinavir values were compared to a predetermined reference range.
- Time since last nelfinavir dose was recorded, and additional demographic data (e.g., HIV RNA, CD4, concomitant medications, weight, medical history) were collected.

Results

- Ten clinic patients were recruited into this pilot study. All subjects were male, median age of 46 years and median weight 71 kg. (Table 1)
- 8 of the 10 were antiretroviral experienced; median # of Pis prior to starting nelfinavir was 2.5 (range 1-3). Baseline CD4 was 261, and median viral load was 4.53 logs.
- At the time that the NFV levels were drawn, subjects had been taking nelfinavir for a median of 6 months, with a range from 2 to 25 months.

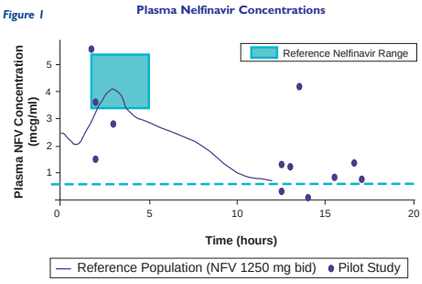
Table 1: Patient Demograhics (n=10)

	Median	Range
Gender	100% male	
Age (yrs)	46	(29-52)
Weight (kg)	71	(61-95)
ARV-experienced	8	
# prior PIs	2.5	(1-3)
Baseline CD4	261	(35-441)
Viral load	4.53	(<50 - >500,000)
Time on NFV (mo)	6	(2-25)

Nelfinavir Concentrations (Figure 1, Table 2)

- Twelve samples were obtained and assessed; median peak nelfinavir value was 3.2 ug/mL, and median trough was 1 ug/mL, which was above the desired target level.
- In total, 50% of the subjects had at least 1 nelfinavir value outside the reference range.

Figure 1



Observed Nelfinavir Concentrations

Table 2

	Peak (n=4)	Trough (n=8)
Ref. Range (ug/mL)	3.3-5.5	>0.7
Median nelfinavir concentration	3.2	1.0
(range)	(1.5-5.6)	(0.1-4.2)
# Outside of Reference Range	3	3
High Nelfinavir Concentrations (n=2)	5.6	4.2
Low Nelfinavir Concentrations (n=3)	2.8	0.1, 0.3

Clinical Response

`Patients with Therapeutic Nelfinavir Concentrations (N=5)`

- 5 subjects had "therapeutic" NFV concentrations, with a median trough of 1.2 ug/mL all were greater than the target value of 0.7 ug/mL
- Of the 5 subjects with therapeutic nelfinavir concentrations, 2 had complete viral responses, defined as viral load <50 copies/mL.
- Both complete responders had viral loads >500,000 copies/mL prior to starting NFV; one was ARV naïve, and the other was using nelfinavir as his 2nd PI-containing regimen.
- In contrast, the 3 non-responders had lower viral loads at baseline prior to starting NFV, with a median viral load of 4.3 logs or ~ 18,000 copies/mL; however, these patients were more heavily pre-treated, and had been on at least 2 or 3 PIs before NFV.
- This *suggests* that despite having adequate NFV levels, these 3 subjects likely had virus that was cross-resistant to NFV at baseline.

`High Nelfinavir Concentrations (N=2)`

- Two subjects had high nelfinavir concentrations, one with an elevated peak value, and one with a very high trough level.
- One patient had a history of hepatitis C with increased LFTs, and was also a known past abuser of alcohol.
- The other subject was on concomitant therapy with ritonavir 300 mg BID and delavirdine, which could have increased NFV levels by inhibiting CYP3A4.
- Both of these individuals experienced significant diarrhea (3-5 BMs/day) which persisted despite aggressive use of antidiarrheal agents including imodium, cotazyme, and calcium carbonate supplements.

`Low Nelfinavir Concentrations (N=3)`

- 3 subjects had low NFV levels (1 had a low peak, 2 had significantly lower troughs)
- One subject had significant diarrhea (5-6 LBMs/day) and likely was not absorbing his NFV since his adherence was excellent
- 2 subjects were receiving concomitant therapy with known enzyme inducers, and 1 was also significantly above his ideal body weight (ABW: 95 kg)
- All initially suppressed (<50 copies/mL), but later had virologic breakthrough on nelfinavir
  - PI-experienced (n=2): median 5 months
  - Antiretroviral naïve (n=1): 16 months

Summary of Results

- In this pilot study, 50% of subjects taking standard nelfinavir doses as part of their antiretroviral regimen had concentrations outside the expected reference range.
- Overall, 3/10 had low nelfinavir levels, and subsequent viral rebound, while 2/10 had high nelfiinavir levels and undesirable toxicity.

Factors that may have contributed to these values included interactions with concomitant medications, malabsorption, and hepatic dysfunction.

Conclusions

- Using the standard recommended adult doses, many patients may experience protease inhibitor levels that fall outside the usual expected range.
- Thus, therapeutic drug monitoring is a promising tool in the management of HIV disease. It may allow for individualization of therapy and potential optimization of outcome.
- TDM may be particularly beneficial when used in a proactive manner, I.e., identifying and correcting for subtherapeutic concentrations prior to viral rebound and possible development of drug resistance

Limitations

- One of the main limitations of this observational cohort study was the use of single time point concentrations, which can be highly variable.
- Although we did make suggestions on dosage modification for patients who had nelfinavir values outside the reference range, either patients had reservations about increasing their dose (possibly due to concerns re: pill burden) or physicians simply changed the antiretroviral regimen altogether.
- From a logistical standpoint, it was sometimes difficult to obtain "true" peak and/or trough levels, because of patient inconvenience. We also had to rely on the accuracy of patient reporting for the time of their last dose, as well as to the type of meal taken with the nelfinavir. This is particularly important since one of the greatest sources of nelfinavir pharmacokinetic variability is the timing and composition of food taken with the dose. Nelfinavir bioavailability decreases by 50% in the absence of food, so if patients have little to no breakfast before taking their NFV dose, then there will be a higher likelihood of low nelfinavir levels.
- Finally, these observations were from a very small cohort of middle-aged male ambulatory clinic patients, who primarily antiretroviral experienced. It is unclear whether these observations may be applied directly to other types of populations.

Future Directions

- In summary, while TDM is an exciting and potentially important tool in the management of HIV disease, there are still many issues that need to be addressed before widespread utilization is feasible:
  - Validate therapeutic ranges for the different protease inhibitors (may be different for naïve vs. experienced patients).
  - Establish which pharmacokinetic variable(s) are best to monitor, and are most predictive of outcome.
  - Identify patients who may be most likely to benefit from TDM, and ensure routine and timely access to assays.
- The pharmacodynamic relationship between drug levels and virologic efficacy should be further explored through prospective studies using TDM in conjunction with other parameters such as viral phenotyping and clinical assessment.

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