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Evaluation of Oral Pancrelipase (Ultrase MT-20) for the Symptomatic Control of Nelfinavir-Associated Diarrhea

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Background

Nelfinavir is a potent HIV protease inhibitor component of highly active antiretroviral therapy. Diarrhea, generally moderate to severe, occurs in an estimated 15 - 20% taking nelfinavir, but generally does not lead to treatment discontinuation. Management strategies for control of diarrhea include use of antimotility agents such as loperamide, psyllium husk, calcium supplements, dietary changes and the empiric use of pancrelipase.

Pancrelipase is clinically indicated in the treatment of chronic diarrhea due to malabsorption in cystic fibrosis (CF) patients. In CF patients, pancrelipase, (which contains amylase, lipase and protease) replaces deficient production of these digestive enzymes, improving nutrient absorption and diarrhea. Dose is adjusted depending on estimated fat intake, and requires dose titration according to clinical response.

Although the mechanism of nelfinavir associated diarrhea is not established, pancrelipase has had reported success as empiric treatment, and is not expected to interfere with absorption of nelfinavir. This study explored clinical features of the impact of pancrelipase therapy, and evaluated potential drug interaction of these agents.

Objectives

- To evaluate the effects of Ultrase MT-20 on the steady state and single dose nelfinavir pharmacokinetics in persons with nelfinavir associated diarrhea who have taken nelfinavir for at least 2 weeks
- To evaluate the safety and efficacy of Ultrase MT-20 in controlling Nelfinavir associated diarrhea
- To evaluate changes in HIV surrogate markers (CD4+ cell count, plasma HIV-RNA) in subjects taking Ultrase MT-20 with nelfinavir combination antiretroviral therapy

Methods

Inclusion Criteria

- Current use of HAART containing nelfinavir 1250 mg twice daily for at least 2 weeks;
- 3 or more loose stools per day attributed to nelfinavir with no alternative explanation evident according to the judgement of the subject's primary care practitioner;
- No GI pathogen evident on stool culture, ova and parasite testing

Exclusion Criteria

- Active gastrointestinal disease or infection within 30 days of screening;
- Current use of more than one HIV protease inhibitor
- Current pregnancy
- History of Pork allergy. Note that this product is derived from pork.

Safety and Efficacy Study

- Open label, multi-site, 12 week study evaluating HIV-infected individuals taking nelfinavir twice daily combination therapy
- All subjects initiated Ultrase MT-20 taken 1-2 capsules with each meal (4 to 8 per day).
- Continued use of antidiarrheal medications was permitted.
- Standardized diarrhea questionnaire self-administered at screening and baseline, weeks 2, 4, 8, 12 study visit to quantify gastrointestinal symptomatology. Following the work of Dr. Talal (Talal, AFCR 1996), we utilized a detailed self-report of gastrointestinal symptoms and stool characteristics during the 24 hours prior to each study visit that assessed stool frequency, color, frequency of bleeding or mucoid stool, severity of urgent need to have a bowel movement (range: 1= none, to 5 = severe), abdominal cramping, presence of large bulky stools, residual rectal stool, stool appearance, and ability to perform tasks of daily living.
- CBC, chemistries, CD4 counts, plasma HIV-RNA evaluated at Baseline, weeks 4 and 12
- Differences in GI symptoms were evaluated using Wilcoxon Signed Rank, as-treated analyses.

Pharmacokinetic Substudy

- Following baseline sampling, and placement of an intravenous catheter, an observed dose of 1250 mg. of nelfinavir was taken with breakfast. A total of 6 samples (hour 0, 1, 2, 4, 8, 12) were collected over 12 hours.
- Twelve hour pharmacokinetics for NFV and its metabolite (M8) were assayed in plasma using HPLC in 5 subjects.
- Differences in NFV and M8 PK parameters were evaluated using Wilcoxon Signed Rank, as-treated analyses.

Table 1

Clinical Characteristics at study entry N=22	
Gender	
Female	36%
Male	64%
Ethnicity	
Caucasion	42%
Hispanic	21%
African American	33%
Other	4%
CD4+ cell count	median 175 cells/mm3 (range 8 – 1066)
Plasma HIV-1 RNA	mean log 2.75 copies/ml (range 1.60 – 4.24)
Use of antimotility agent	57%

Table 2

Patient Management	number
Initiated pancrelipase	22
Discontinued prior to week 12	8
Lack of treatment efficacy	8
Additional basis for discontinuation: viral hepatitis (1) Increased diarrhea and history of pork allergy (1)	

- No other adverse events attributable to Ultrase MT 20.

Results

Safety and Efficacy Study

- Mild clinical benefit is suggested by the trend to less stool frequency at weeks 4 and 8 ($p > 0.05$), with significant improvement at week 12 ($p = 0.03$).
- Significant improvement in urgency is evident at weeks 4, 8 and 12 ($p < 0.05$).
- No significant improvements occurred in abdominal cramps, or ability to perform daily tasks (data not shown).
- Use of antimotility agents remained steady or decreased in study subjects. A single subject reported increased use of an antimotility agent at week 2, and dropped out before week 4.
- No significant changes in CD4+ cell count, viral load or safety labs (hematology and chemistries) were evident during this study. All individuals entering with pl. HIV RNA below 400 copies/ml remained in that range at the next assessment. Plasma HIV RNA in subjects with detectable values at study baseline showed no clear trend toward viral rebound (Table 4). 5 of 7 (71%) had lower pl. HIV RNA at the next assessment.

Pharmacokinetic Substudy

- Steady state PK of NFV was evaluated in 5 subjects at baseline and 14-28 days after initiation of pancrelipase.
- Significant inter-patient variability in PK parameters was observed.
- NFV AUC, Cmin, Cmax, and Tmax, were slightly reduced ($p > 0.05$) after initiation of pancrelipase. A trend to lower NFV M8 metabolite levels did not reach statistical significance.

Results continued

Table 3
Gastrointestinal Symptoms by Self Report (Mean values)

	week -2	week 0	week 2	week 4	week 8	week 12
Stool Frequency /24 hours	4.4	4.3	2.4	3.0	2.8	2.4*
Urgent bowel movements (None = 0, Maximum severity=5)	3.2	3.4	1.9	1.9*	2.0*	1.8*
Abdominal Cramps (None =0, Max severity=5)	2.2	1.9	1.6	1.1	1.1	1.2
Data available (n)	20	18	10	16	12	11

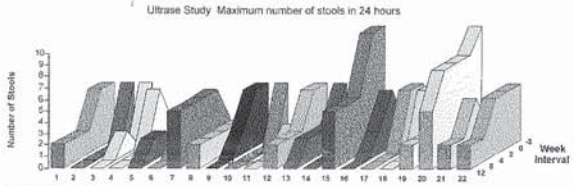
* = $p < 0.05$

Table 4
Plasma HIV-1 RNA in 8 subjects detectable at study entry

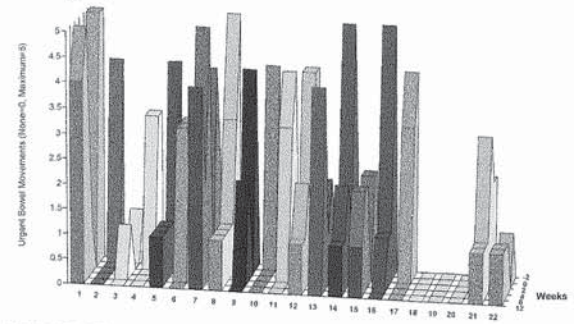
Baseline	week 4	week 12
3510	10,100	discontinued
1240	718	> 75,000*
14000	16,600	> 75,000*
1180	2550	715
572	4020	discontinued
10,600	discontinued	
5490	2100	discontinued
1950	1040	1240

* Nelfinavir non-adherence

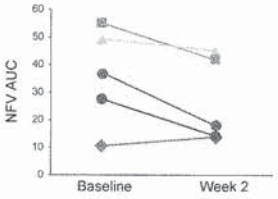
Stool Frequency



Stool Urgency

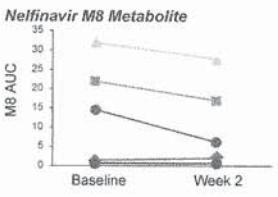


NFV AUC Differences



NFV AUC	Baseline	Week 2
Mean	31.16	23.07
Median	36.51	17.76
Min	10.29	13.75
Max	54.83	45.09

Nelfinavir M8 Metabolite



M8 AUC	Baseline	Week 2
Mean	7.41	4.60
Median	14.01	6.09
Min	0.60	0.40
Max	31.83	27.72

Conclusions

- **The use of pancrelipase was well tolerated and associated with improvement in the urgent need for a bowel movement, and the frequency of bowel movements in many subjects. Subjects continuing in the study generally reported clinical benefit.**
- **In this open label, uncontrolled study, drop out was frequent (37%) and often associated with lack of perceived benefit of treatment of diarrhea.**
- **Significant interpatient variability in PK parameters of NFV was observed in the 5 subjects evaluated. Unlike previous studies of pancrelipase and nelfinavir, this small PK substudy found moderate declines in AUC of NFV and M8, raising concern for possible interference with drug absorption. Previous studies by Razzeca (CROI 1998, poster 12383, n=4), and Price (1999) have demonstrated no PK interaction between pancrelipase and nelfinavir.**
- **Use of pancrelipase for nelfinavir associated diarrhea was not associated with viral rebound.**

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The opinions of the author do not reflect those of Agouron Pharmaceuticals, Inc., A Pfizer Company