

STEADY-STATE INDINAVIR (CRIKIVAN®) PHARMACOKINETICS IN CEREBROSPINAL FLUID AND PLASMA IN PATIENTS RECEIVING CONCOMITANT LOW-DOSE RITONAVIR (NORVIR®), AS DETERMINED BY ULTRA-INTENSIVE CSF SAMPLING

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INTRODUCTION

The central nervous system (CNS) is involved by HIV-1 during all stages of HIV disease. Before the availability of potent antiretroviral agents, dementia was common during advanced AIDS. Fortunately, the widespread use of potent therapy has been associated with declines in overt neurological manifestations. However, not all patients prescribed antiretroviral therapy maintain adequate control of viral replication. P-glycoprotein in the blood-brain barrier may limit entry of some protease inhibitors into the CNS. Failure to control HIV-1 in the brain may contribute to virologic failure in peripheral compartments and lead to neurologic complications. We previously characterized indinavir penetration into CSF in the absence of pharmacokinetic "boosting". In the present study we used ultra-intensive CSF and plasma sampling to provide detailed characterization of indinavir disposition into CSF among patients receiving concomitant low-dose ritonavir.

OBJECTIVES

- To characterize steady-state indinavir pharmacokinetics in CSF and plasma in adults with HIV infection receiving indinavir (800 mg q12h) and ritonavir (100 mg q12h).
- To characterize relationships between total and free drug concentrations (not bound to proteins) in both CSF and plasma.
- To characterize the pharmacokinetics of indinavir transfer from plasma to CSF.
- To compare the pharmacokinetics of Indinavir administered concomitantly with Ritonavir to those observed in a previous study of Indinavir without concomitant Ritonavir.

ELIGIBILITY CRITERIA

- Adults (≥ 18 yrs of age) who initiated HIV therapy through participation in Merck Protocol 094.
- Patients judged by primary care physician as likely to be highly compliant with study therapy.
- Patient on stable therapy with indinavir, zidovudine, zalcitabine, and 3TC for 2 weeks.
- Patient meeting defined criteria for screening ECG, chest X-ray, urinary drug screen, hematology, chemistry, and coagulation studies.
- Patient willing and able to provide written informed consent.

METHODS

Drug Administration

- All antiretroviral medications were given concomitantly:
 - Indinavir 800 mg q12h
 - Ritonavir 100 mg q12h
 - d4T 40 mg q12h
 - 3TC 150 mg q12h

CSF and Plasma Sampling

- Cerebrospinal fluid was collected through an 18-gauge indwelling lumbar intrathecal catheter.
- CSF and plasma samples were collected at 0, 0.5, 1, 2, 3, 4, 6, 8, and 12 hours post-dose.
- Plasma and CSF were stored at -70°C until assayed.

Quantification of Total and Free Indinavir

- Indinavir was quantified by a validated LC/MS/MS method (BAS Analytics, West Lafayette, IN).
- Free indinavir was separated by ultrafiltration. Protein binding determinations were performed on one plasma and one CSF sample per subject.

Pharmacokinetic Analysis

- The AUC was calculated by the modified trapezoidal method using stable piecewise cubic polynomials.
- Statistical analysis were performed using SPSS version 9.0 (Chicago, IL).

The Blood-Brain Barrier and Immune Activation

- CSF-to-plasma albumin quotient was calculated as: $(\text{albumin}_{\text{CSF}} \div \text{albumin}_{\text{plasma}})$. The blood-brain barrier was intact if <0.0074 .
- The CSF IgG index was calculated as: $(\text{IgG}_{\text{CSF}} \div \text{IgG}_{\text{plasma}}) \div (\text{albumin}_{\text{CSF}} \div \text{albumin}_{\text{plasma}})$. Intracerebral IgG production was present if >0.66 .
- A CSF β -2-microglobulin concentration >2 mg/L indicated immune activation.

Table 1. Characteristics of Study Subjects at Time of Ultra-Intensive CSF and Plasma Sampling

Characteristic	Study Subject						
	A	B	C	D	E	F	G
CD4 (cells/mm ³)	225	233	68	410	88	328	237
CSF values							
WBCs (per mm ³)	0	3	2	4	1	2	7
RBCs (per mm ³)	16	0	0	145	355	0	1
Protein (mg/dL)	46	65	33	33	31	30	41
Glucose (mg/dL)	69	74	56	64	54	64	62
β 2M (mg/L)*	1.1	2.9	0.9	1.3	1.4	1.0	1.5
CSF IgG index	0.38	0.83	0.52	0.62	0.70	0.55	0.74
CSF/plasma alb.	0.0051	0.0089	0.0052	0.0049	0.0035	0.0027	0.0033

* β 2M = beta-2-microglobulin.

Table 2. Selected Pharmacokinetic Parameters of Free and Total Indinavir

Parameter	Total Indinavir		Free Indinavir	
	Mean (S.D.)	Range	Mean (S.D.)	Range
Free proportion				
Plasma, %	—	—	55.9 (4.1)	50.1 – 60.9
CSF, %	—	—	98.6 (1.3)	97.0 – 100.0
AUC _{0-12h}				
Plasma, nM·hr	68913 (23302)	50404 – 117049	38829 (15124)	26614 – 71283
CSF, nM·hr	6606 (2481)	3903 – 11385	6502 (2397)	3903 – 11043
CSF/plasma, %	9.9 (3.3)	7.4 – 16.6	17.5 (6.4)	12.8 – 31.4
C _{max}				
Plasma, nM	13493 (2819)	7594 – 15744	7521 (1580)	4404 – 9069
CSF, nM	746 (241)	409 – 1132	753 (233)	409 – 1098
C _{min}				
Plasma, nM	1243 (1217)	534 – 3972	719 (758)	282 – 2419
CSF, nM	285 (136)	153 – 544	280 (131)	149 – 527
T _{max}				
Plasma, hours	1.0 (0.3)	0.5 – 1.5	1.0 (0.3)	0.5 – 1.5
CSF, hours	5.3 (1.3)	3.0 – 6.0	5.3 (1.3)	3.0 – 6.0

Table 3. Effect of Low-Dose Ritonavir on Indinavir Pharmacokinetic Parameters: Total Daily IDV dose (1,600 mg with RTV) vs (2,400 without RTV)

Parameter	Total Indinavir	
	Mean (SEM)	P value
Plasma (% of prior value) ^a		
AUC _{0-24h} ^c	171 (24)	.005
C _{max}	97 (12)	.563
C _{min}	528 (184)	.002
CSF (% of prior value)		
AUC _{0-24h} ^c	250 (35)	.001
C _{max}	262 (43)	.003
C _{min}	270 (47)	.002
CSF-to-plasma AUC _{0-24h} ratio (% of prior value)		
Total drug	148 (19)	.008
Free drug	103 (15)	.563
Time to C _{max} (difference in hours)		
Plasma	0.09 (0.21)	.505
CSF, hours	1.19 (1.7)	.011

^a Compared to our previous study (Clin Pharm Therap 2000;68:367).^b Percentage of prior value was calculated by dividing values from the present study by values from the previous study. 100% is no change.^c AUC_{0-24h} was estimated by multiplying AUC_{0-8h} and AUC_{0-12h} by three and two, respectively.

Figure 1. CSF and Plasma Indinavir Levels in Each Subject and Group Means

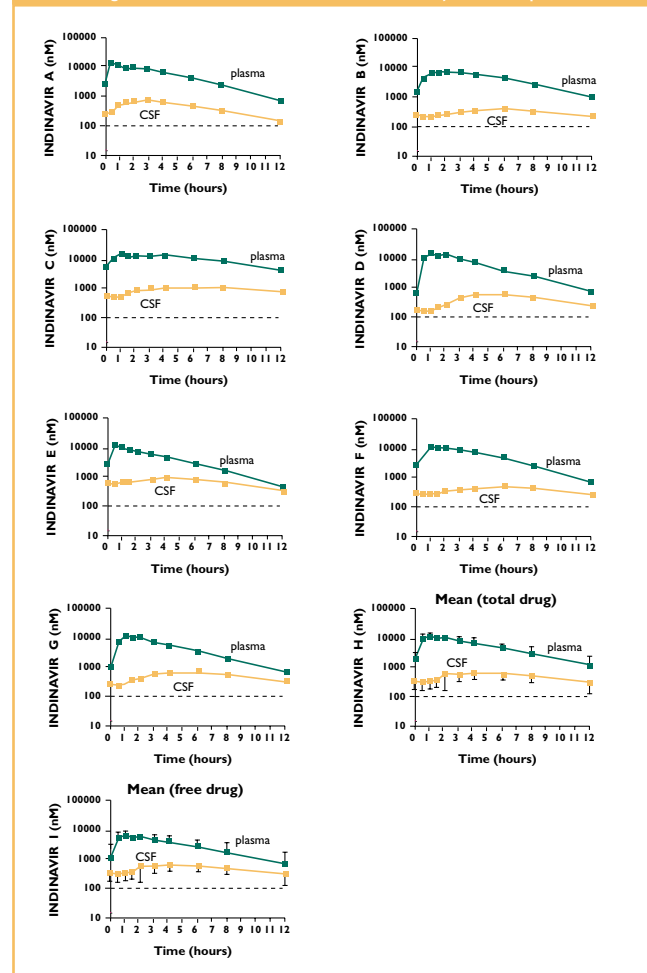
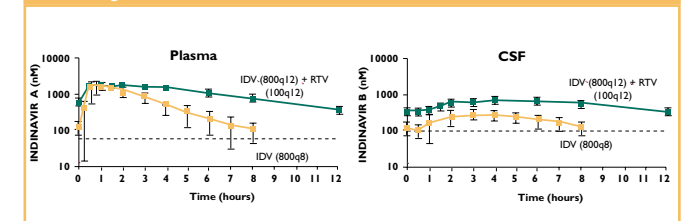


Figure 2. Indinavir Concentration Profiles With and Without Low-Dose Ritonavir



RESULTS

- All 7 subjects had been receiving indinavir-based therapy for at least 2 weeks.
- Four subjects had normal indices of blood-brain barrier integrity without evidence of intrathecal immune activation (Table 1).
- Plasma indinavir concentrations generally achieved C_{max} within 1 hour post-dose, while C_{max} in CSF occurred at 5.3 hours (Table 2).
- Total indinavir levels in CSF exceeded 100 nM (I_{C₅₀ of wild-type HIV is 50-100 nM) during the entire dosing interval in all subjects at all timepoints (Figure 1).}
- In CSF, 98.6% \pm 1.3% of drug was free. In plasma 55.9% \pm 4.1% was free (Table 2 and Figure 2).
- The CSF-to-plasma AUC_{0-12h} ratio for free indinavir was 17.5% \pm 6.4%.
- The trough indinavir concentration in CSF was 285 nM \pm 136 nM.
- CSF indinavir AUC_{0-12h} correlated significantly with total plasma C_{max} (r=0.77, P=0.044) and free plasma C_{max} (r=0.77, P=0.043), and tended to correlate with total plasma indinavir AUC_{0-12h} (r=0.72, P=0.068) and free plasma AUC_{0-12h} (r=0.74, P=0.059).
- CSF indinavir AUC_{0-8h} did not correlate with indices of blood-brain barrier integrity or intrathecal immune activation.
- Low-dose ritonavir increased CSF indinavir AUC_{0-24h}, C_{max}, and C_{min} by 2- to 3-fold compared to our previous study of indinavir (800 mg q8h) without ritonavir (Clin Pharm Therap 2000;68:367). This was despite a lower total daily indinavir dose.

CONCLUSIONS

- With regard to indinavir penetration, the CSF is a slowly equilibrating compartment relative to plasma.
- Free indinavir accounted for 98.6% of drug in cerebrospinal fluid and 55.9% in plasma.
- Mean CSF C_{max}, C_{min}, and AUC_{0-12h} values for free indinavir were 811 nM, 280 nM, and 6502 nM·hr, respectively.
- Free indinavir levels in CSF exceeded 140 nM in every patient at all timepoints.
- The CSF-to-plasma AUC_{0-12h} ratio for free indinavir was 17.5% \pm 6.4%.
- This intensive sampling data will allow detailed modeling of the effect of low-dose ritonavir on the barrier to indinavir penetration into the CNS.
- Low-dose ritonavir administered twice daily with indinavir increases CSF indinavir concentrations 2- to 3-fold compared to thrice-daily indinavir without ritonavir despite a lower total daily indinavir dose. This should enhance control of HIV in the CNS.