Pharmacokinetics of Indinavir at 800, 600, and 400 Milligrams Administered with Ritonavir at 100 Milligrams and Efavirenz in Ethnic Chinese Patients Infected with Human Immunodeficiency Virus

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We assessed the pharmacokinetics of three different doses of indinavir in five patients. All doses achieved trough concentrations above efficacy thresholds. Toxic trough concentrations were observed in all patients receiving 800 mg, in two patients receiving 600 mg, and in none receiving 400 mg. Indinavir at 400 mg may be efficacious and less toxic in patients taking ritonavir and efavirenz.

Coadministration of ritonavir increases concentrations of indinavir and prolongs indinavir's half-life (10, 13). Indinavir (800 mg) is now commonly prescribed with ritonavir in doses of 100 mg twice daily. The higher drug concentrations of indinavir in ritonavir-boosted regimens may increase toxicity, especially nephrolithiasis (2). Lower doses of indinavir may provide clinically efficacious drug concentrations while minimizing toxicity and lowering costs.

The combination of efavirenz and indinavir has durable efficacy similar to that of dual nucleosides and indinavir (6, 12). However, efavirenz reduces levels of indinavir by about 20% (1); it is recommended that indinavir be increased to 1,000 mg when coadministered with efavirenz (Crixivan product monograph, Merck & Co.). However, boosting with ritonavir may allow indinavir doses to be maintained or even reduced. Two studies show adequate trough levels but potentially toxic peak levels with 800 mg of indinavir boosted with ritonavir, even when this combination is coadministered with efavirenz (1, 3). Dose reductions of indinavir may provide better toxicity profiles.

We recruited human immunodeficiency virus-infected patients on a regimen of indinavir, ritonavir, and efavirenz and with undetectable viral loads. The study was performed at Tan Tock Seng Hospital, Singapore, Republic of Singapore, and approved by the local Ethics Committee.

Patients' doses were established at 800 mg of indinavir and 100 mg of ritonavir twice daily for at least 1 week before the study. Twelve-hour pharmacokinetic protocols were performed at baseline and 1 week after dose reductions to 600 and 400 mg of indinavir twice daily. Subjects then returned to taking indinavir (800 mg).

Patients arrived before 8 a.m. on each pharmacokinetic profile day, some on the day before. They were given their morning doses of indinavir and ritonavir with standardized medium-fat, medium-calorie breakfasts consisting of 465 kcal (33% fat,

20% protein, and 47% carbohydrate). Blood was collected for drug concentration measurements at 0 (baseline), 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 12 h post-indinavir ingestion.

Indinavir concentrations were measured by high-performance liquid chromatography–tandem mass spectrometry as previously described (10a). Pharmacokinetic parameters, including peak and trough concentrations (C_{max}s and C_{min}s, respectively) of indinavir, areas under the curve, half-lives, and times to maximum concentration, were obtained by using TOPFIT software (Gustav Fischer Verlag, Stuttgart, Germany).

We used the efficacy threshold indinavir C_{min} of 100 ng/ml, based on Department of Health and Human Services consensus guidelines (9). We used the toxicity threshold indinavir C_{min} of 500 ng/ml, based on a nephrotoxicity study (11). We used the toxicity threshold indinavir C_{max} of 10,000 ng/ml, based on a Thai study (3a).

Drug concentrations were compared among the three dosage regimens with the nonparametric Friedman test for three related samples by use of SPSS version 11.0 (SPSS Inc., Chicago, Ill.).

We recruited five subjects, all ethnic Chinese males, from whom we obtained 15 full pharmacokinetic profiles. The median age was 50 years (range, 33 to 59 years), the median body weight was 65 kg (range, 46 to 76 kg), and the median CD4 count was 415×10^6 cells/liter (range, 161×10^6 to 505×10^6 cells/liter). Concomitant medications (none of which interact with indinavir) were kept unchanged throughout the study period. Self-reported adherence was greater than 95%.

The results are shown in Tables 1 and 2. Median indinavir C_{max}s measured in patients on doses of 600 mg (4,909 ng/ml) and 400 mg (2,986 ng/ml) were significantly lower, by 38 and 63%, respectively, than those of patients on doses of 800 mg (7,965 ng/ml) ($P = 0.007$). With the doses of 800 and 600 mg, one subject had a C_{max} above 10,000 ng/ml, compared to no subjects on 400 mg with a C_{max} above this level.

Evening C_{min}s (C_{12h}s) were consistently and on average 54% lower than the morning C_{min} (C_{0h}s) ($P = 0.001$). Median C_{0h}s of patients on 600 mg (295 ng/ml) and 400 mg (336 ng/ml) were significantly lower, by 75 and 71%, respectively, than C_{0h}s of

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TABLE 1. Plasma indinavir PK parameters over 12 h for three different doses[a]

| Patient or parameter | C_{max} (ng/ml) | | | C_{min} | | | | | | AUC_{0-12}[b] (ng · h/ml) | | |
| | | | | C_{0h} | | | C_{12h} | | | | | |
	800/100[c]	600/100	400/100	800/100	600/100	400/100	800/100	600/100	400/100	800/100	600/100	400/100
1	7,965	4,348	2,375	1,317	295	213	447	212	170	45,467	22,589	12,726
2	7,336	4,881	2,986	1,157	583	336	501	283	105	43,745	26,464	14,237
3	7,596	4,909	3,120	510	287	289	172	108	124	35,691	20,842	14,515
4	8,149	7,789	2,939	820	228	404	380	199	135	47,944	26,249	16,234
5	17,316	11,696	5,863	1,565	1,242	370	964	357	303	85,640	52,516	25,954
Median	7,965	4,909	2,986	1,157	295	336	447	212	135	45,467	26,249	14,515
Mean	9,672	6,725	3,457	1,074	527	322	493	232	167	51,697	29,732	16,733
SD	4,285	3,090	1,375	415	423	74	291	94	79	19,522	12,961	5,303

[a] P values for comparisons of parameters were all less than 0.01.
[b] AUC, area under the indinavir pharmacokinetic curve.
[c] Doses (given twice daily) are given in milligrams of indinavir/milligrams of ritonavir.

patients on 800 mg (1,157 ng/ml) ($P = 0.022$). All five subjects on doses of 800 mg had indinavir C_{0h}s above the 500-ng/ml toxicity threshold, compared to two and no patients on doses of 600 and 400 mg, respectively. With doses of 800 mg, two subjects had indinavir C_{12h}s above 500 ng/ml, compared to no subjects on the lower doses. None of the subjects had C_{0h}s or C_{12h}s below 100 ng/ml on any dose.

The median indinavir half-life was about 2 h, while the time to C_{max} was about 3 h, with no significant differences between results for patients on different doses. Viral loads remained undetectable (<50 copies/ml) in all subjects.

We found that all patients on doses of 800 mg had toxic indinavir C_{min}s and/or C_{max}s, compared to two patients on 600 mg and none on 400 mg. Toxic C_{min}s were also observed in a pharmacokinetic study of indinavir (800 mg) boosted with efavirenz in human immunodeficiency virus-infected patients (3). Our concentrations achieved with lower doses of indinavir were favorable in terms of likely risk of toxicity.

We found substantial differences between C_{0h}s and C_{12h}s (the morning and evening C_{min}s). This difference is unlikely to be explained by later dosing at night, since our subjects confirmed their compliance with instructions to take the night doses at 8 p.m. The difference was observed consistently on all three study days, and the same result was found in subjects admitted the previous day, when we timed their evening dose. This difference most likely reflects diurnal variation in indinavir concentrations, a phenomenon that has been previously noted for indinavir as well as for other protease inhibitors (PIs) (7, 8). In light of this difference, it would be advisable for all future research studies of PIs to include measurements of both morning and evening C_{min}s.

The C_{12h}s were close to the consensus efficacy threshold in several patients on 400-mg doses. This finding raises the theoretical concern that there might be higher risks of developing resistance, although the significance in patients with fully suppressed viral replication is uncertain. The mean C_{12h}s of patients on 600- and 400-mg doses were 63 and 4% higher than the C_{12h}s of those on the standard unboosted indinavir dose (Crixivan product monograph, Merck & Co.). Thus, even with a regimen of 400 mg, the efficacy should still be comparable to that of unboosted indinavir. A small group of patients with undetectable virus loads switching from unboosted indinavir to 400 mg of indinavir with ritonavir given twice daily maintained viral suppression at 48 weeks (5). In contrast, in patients with detectable viral loads and previous PI exposure, switching to 400 mg of indinavir resulted in some treatment failures (7). Therefore, the 400-mg dose of indinavir may best be avoided for patients who have previously experienced PI failure, in whom the 95% inhibitory concentration may be raised above that for a wild-type virus (4). Furthermore, for PI-naïve patients, it may be prudent to initiate therapy with higher doses of indinavir and to reserve dose reduction for patients who have demonstrated good adherence to therapy and have achieved undetectable viral loads.

The results of our study, taken together with existing literature, suggest that 400 mg of indinavir, 100 mg of ritonavir, and 600 mg of efavirenz may be an effective, nontoxic, and relatively economical treatment regimen for patients who do not have preexisting PI resistance. This regimen deserves further evaluation in comparative clinical trials.

TABLE 2. Plasma indinavir PK parameters and threshold values for three different doses

| Dose[a] | No. (%) of patients with indicated toxicity threshold | | | | |
	C_{max} of >10,000 ng/ml	C_{0h} of >500 ng/ml	C_{12h} of >500 ng/ml	C_{0h} of <100 ng/ml	C_{12h} of <100 ng/ml
800/100	1/5 (20)	5/5 (100)	2/5 (40)	0/5 (0)	0/5 (0)
600/100	1/5 (20)	2/5 (40)	0/5 (0)	0/5 (0)	0/5 (0)
400/100	0/5 (0)	0/5 (0)	0/5 (0)	0/5 (0)	0/5 (0)

[a] Doses (given twice daily) are given in milligrams of indinavir/milligrams of ritonavir.

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