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Pharmacokinetics of Intravenous Itraconazole in Stable Hemodialysis Patients

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The pharmacokinetics of intravenous itraconazole (ITC) was studied in dialysis patients. Dialysis had no effect on the half-life and clearance of ITC or OH-ITC. However, dialysis allowed the clearance of hydroxypropyl-β-cyclodextrin (HP-β-CD). The area under the concentration-time curve from time zero to infinity ($AUC_{0-\infty}$) for HP-β-CD administered before dialysis was lower than the $AUC_{0-\infty}$ when it was administered after dialysis ($P < 0.01$). Administration of ITC intravenously just prior to hemodialysis appears to produce adequate systemic exposures of ITC and OH-ITC while allowing dialysis clearance of HP-β-CD. Studies of multiple administrations are warranted.

The injectable formulation of itraconazole (ITC) was licensed in the United States in 1999 on the basis of evidence that this formulation achieves adequate levels in blood more rapidly and with less patient-to-patient variability than does the orally administered preparation of the drug (1, 6, 9, 10). Intravenously administered (i.v.) ITC is formulated in a molecular encapsulation mechanism using hydroxypropyl-β-cyclodextrin (HP-β-CD) allowing the delivery of sparingly soluble drugs (2, 5).

ITC is metabolized predominantly by the cytochrome P450-3A4 isoenzyme system, resulting in the formation of several metabolites, including OH-ITC, the major active metabolite (2). Not surprisingly, concentrations of ITC in the plasma of patients with mild to moderate renal insufficiency have been comparable to those obtained in healthy individuals (K. Plaisance, H. Zhou, P. Lee, A. Hassell, J. Wu, S. Travers, K. Chan, and L. Pesco-Koplowitz, 99th Annu. Meet. Am. Soc. Clin. Pharmacol. Ther., abstr. PII-40, 1998).

On the other hand, the principal route of elimination of HP-β-CD is glomerular filtration and total clearance correlates with the glomerular filtration rate (10). Patients with severe renal impairment (creatinine clearance of ≤19 ml/min) show a significant increase in the concentration of the drug in plasma and decreased elimination of HP-β-CD (data on file, Janssen Research Foundation). As a consequence of these data and the relatively limited data in general on the behavior of ITC, OH-ITC, and HP-β-CD in patients with severe renal failure, the licensure of the i.v. preparation of ITC is limited to its use in patients with a creatinine clearance of ≥30 ml/min (Sporanox [ITC] package insert, 2002, Janssen Pharmaceutica, Beerse, Belgium).

The objective of this study was to evaluate the pharmacokinetic profile of single-dose i.v. infusions of ITC before and after dialysis in subjects undergoing chronic maintenance hemodialysis.

Four adult patients with end stage renal disease who had been receiving the same hemodialysis regimen for a period of at least 4 weeks were enrolled in the study. The study was reviewed and approved by the University of Texas Medical School Houston Institutional Review Board. Written informed consent was obtained from each patient. Patients were excluded if they used astemizole, atorvastation, carbamazepine, clarithromycin, cisapride, lovastatin, isoniazid, midazolam, phenytoin, phenobarbital, pimozide, quinidine, quinine, rifampin, rifabutin, simvastatin, terfenadine, or triazolam in the 15 days before enrollment; had a requirement for any of these drugs during the study period; had a serum pyruvic glutamic transaminase or glutamic oxalacetic transaminase level four or more times the upper limit of normal at baseline; were pregnant; or were breastfeeding. Patients were also instructed not to consume alcoholic beverages and to refrain from jogging and strenuous exercise during the study period.

Patients received two separate 200-mg doses of i.v. ITC with each dose containing 8 g of HP-β-CD administered via a syringe pump over a period of 1 h at an interval of no less than 6 weeks. The study used a crossover design: all subjects received both doses, with half of the subjects receiving the predialysis dose as the first dose and the other half receiving the postdialysis dose as the first dose.

Venous blood samples were obtained to determine the pharmacokinetic profiles of ITC, OH-ITC, and HP-β-CD. Dialysate samples for determination of HP-β-CD were collected during the dialysis session, and urine samples were collected throughout the study period. All serum, urine, and dialysate samples were stored at or below −70°C until assayed.

Calibration standards, controls, and plasma samples were

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TABLE 1. Pharmacokinetic parameters of ITC, OH-ITC, and HP-β-CD before dialysis, after dialysis, interdialysis, and intradialysis[a]

Compound and parameter	BD	AD	ID	HD
ITC				
C_{max} (ng/ml)	1,980 ± 659	1,889 ± 1,237	NA[b]	NA
V (liters/kg)	17.5 ± 11.6	9.4 ± 2.8	NA	NA
$AUC_{0-\infty}$ (ng · h/ml)	8,047 ± 7,640	6,293 ± 3,707	NA	NA
k_e (h^{-1})	0.07 ± 0.06	0.06 ± 0.01	0.07 ± 0.04	0.14 ± 0.09
$t_{1/2}$ (h)	19.7 ± 16.2	12.0 ± 2.0	14.6 ± 8.5	14.7 ± 24.1
OH-ITC				
C_{max} (ng/ml)	269 ± 96	408 ± 181	NA	NA
$AUC_{0-\infty}$ (ng · h/ml)	13,236 ± 21,111	9,523 ± 6,886	NA	NA
k_e (h^{-1})	0.07 ± 0.05	0.06 ± 0.04	0.06 ± 0.03	0.07 ± 0.05
$t_{1/2}$ (h)	14.5 ± 9.8	19.7 ± 15.9	15.6 ± 6.9	17.0 ± 15.0
HP-β-CD				
C_{max} (ng/ml)	662 ± 171	773 ± 265	NA	NA
V (liters/kg)	0.21 ± 0.03	0.30 ± 0.09	NA	NA
$AUC_{0-\infty}$ (ng · h/ml)[c,d]	5,485 ± 2,202	30,282 ± 12,098	21,638 ± 8228[e]	817 ± 262[f]
k_e (h^{-1})[d]	NA	NA	0.02 ± 0.01	0.32 ± 0.18
$t_{1/2}$ (h)[d]	NA	NA	33.3 ± 12.0	2.9 ± 1.5
CL[g] (liters/h)[d]	NA	NA	0.41 ± 0.14	2.25 ± 1.46

[a] Values are reported as the mean ± the standard deviation. BD, dose administered before dialysis; AD, dose administered after dialysis; ID, interdialysis period (between dialysis sessions); HD, intradialysis period (during dialysis sessions).
[b] NA, not applicable.
[c] AD versus BD, $P < 0.05$.
[d] HD versus ID, $P < 0.05$.
[e] AUC_{id}.
[f] AUC_{hd}.
[g] CL, clearance.

assayed for ITC and OH-ITC by a modified and validated reverse-phase high-performance liquid chromatography (HPLC) method as previously described (8). The testing range for ITC and OH-ITC by HPLC is 0.01 to 5.0 μg/ml. The lower limit of quantitation is 0.01 μg/ml. The extraction recovery rate is approximately 90% for ITC and approximately 89% for OH-ITC. The ITC interday coefficients of variation for controls (0.05, 0.25, and 2.5 μg/ml) were 4.8, 4.4, and 6.7%, respectively. The OH-ITC control coefficients of variation (0.05, 0.25, and 2.5 μg/ml) were 5.7, 5.9, and 5.0%, respectively.

HP-β-CD concentrations were measured by HPLC at the Janssen Research Foundation, Beerse, Belgium, as previously described (3).

Noncompartmental pharmacokinetic analyses were conducted for ITC, OH-ITC, and HP-β-CD with PK Solutions 2.0 (Summit Research Services, Montrose, Colo.). The elimination rate constant (k_e) and half-life ($t_{1/2}$) were determined from the terminal portion of the serum concentration-time curve for both the interdialysis (between dialysis sessions) and intradialysis (during dialysis sessions) time periods. The interdialytic elimination rate constant (k_{eid}) was calculated as the ln (60 min postinfusion concentration/pre-hemodialysis concentration)/interdialysis time, and the intradialytic elimination rate constant was calculated as the ln (pre-hemodialysis concentration/end-of-hemodialysis concentration)/intradialysis time. The area under the curve (AUC) was calculated by the trapezoidal rule. The AUC for the interdialysis period (AUC_{id}) and the AUC for the intradialysis period (AUC_{hd}) were calculated from the postdialysis and predialysis concentration-time curves, respectively. The apparent volume of distribution (V) was calculated as the dose/AUC_{id} · k_{eid} and expressed as liters per kilogram of actual body weight. The nondialysis or intrinsic clearance was calculated as the dose divided by the AUC for the interdialysis period. Dialysis clearance was calculated as the amount of drug removed by hemodialysis divided by the AUC_{hd}.

Pre- and postdialysis pharmacokinetic parameters and intradialysis and interdialysis pharmacokinetic parameters were analyzed by one-way analysis of variance. Statistical significance was defined as $P < 0.05$.

Dialysis parameters for all patients were a blood flow rate of 400 ml/min, a dialysate flow rate of 800 ml/min, and a dialysis time of 3 to 4 h. All patients were dialyzed with an F-80 filter (Fresenius Medical Care, Bad Homburg, Germany). Neither ITC nor OH-ITC was recovered from the urine or ultrafiltrate.

The mean pharmacokinetic parameters for ITC, OH-ITC, and HP-β-CD when i.v. ITC was administered before, after, and during hemodialysis are outlined in Table 1. The pharmacokinetics of ITC and OH-ITC were not affected by hemodialysis. There was no difference in the maximum concentration in serum (C_{max}) or V of HP-β-CD when i.v. ITC was administered before or after hemodialysis. There was, however, a significantly higher $AUC_{0-\infty}$ of HP-β-CD when i.v. ITC was administered after hemodialysis, and hemodialysis was responsible for an average of 84% of the total clearance of HP-β-CD. Figure 1 illustrates the concentration-time curve for the mean concentrations of HP-β-CD when i.v. ITC was administered before and after dialysis.

In our study of i.v. ITC administered to patients with stable, chronic renal failure on hemodialysis, dialysis had no effect on the pharmacokinetic profiles of ITC and OH-ITC and the observed drug levels in plasma were similar to those seen in

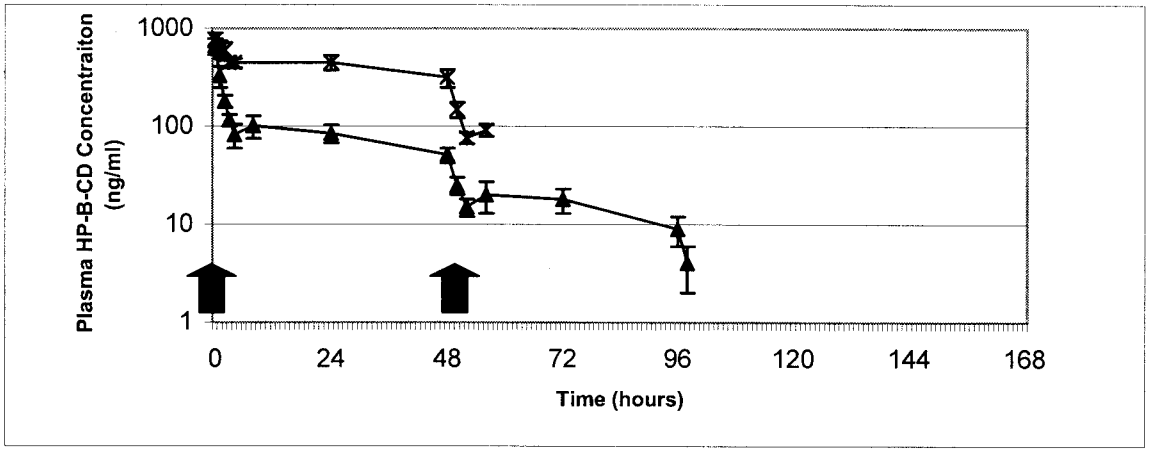

FIG. 1. Mean HP-β-CD concentration-versus-time profiles (± standard error) of i.v. ITC administered before (▲) and after (×) dialysis. ↑, dialysis.

other populations (9). In patients with normal renal function the terminal half-lives of both ITC and OH-ITC are approximately 20 to 24 h after administration of a single dose of i.v. ITC (7). This is consistent with ITC's primary hepatic route of metabolism and elimination. Dose adjustment is thus unnecessary in patients with renal failure, and dialysis is not effective in removing ITC in the event of an overdose (Sporanox [ITC] package insert).

Dialysis did, however, significantly remove the HP-β-CD component of i.v. ITC. Previous data on subjects with normal renal function reported the $t_{1/2}$ of HP-β-CD to be 2.5 ± 0.84 h (data on file, Janssen Research Foundation). However, in patients with severe renal impairment, the $t_{1/2}$ of HP-β-CD was 15.6 ± 6.0 h and the total clearance was 0.67 ± 0.2 liter/h (data on file, Janssen Research Foundation), values that are consistent with our data. Therefore, our data demonstrate that hemodialysis was capable of clearing HP-β-CD as efficiently as a patient with normal renal function.

Since the physiochemical and intradialysis pharmacokinetic properties vary between different azoles and cyclodextrins (4; Vfend [voriconazole] package insert, 2003, Pfizer Inc., New York, N.Y.), our findings should not be extrapolated to other drugs that use other forms of cyclodextrin as carriers.

In conclusion, the pharmacokinetic profile of ITC or OH-ITC after administration of a single dose of i.v. ITC is not affected by hemodialysis. However, hemodialysis significantly removes the HP-β-CD carrier of i.v. ITC. This supports a predialysis administration strategy for i.v. ITC. Further studies with multiple administrations, larger study population, and other forms of dialysis are needed.

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