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NOTES

Steady-State Pharmacokinetics of Imipenem in Febrile Neutropenic Cancer Patients

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We ascertained the pharmacokinetics of imipenem in febrile granulocytopenic cancer patients. The values observed were both different from and significantly more variable than those observed in normal volunteers. Free drug concentrations exceeded the MIC for 90% of *Escherichia coli*, *Klebsiella pneumoniae*, and *Staphylococcus aureus* strains for greater than 6 h. The MIC for 90% of *Pseudomonas aeruginosa* strains was exceeded for 4 h. Because imipenem induces a 2-h postantibiotic effect in *P. aeruginosa*, it is promising as single-agent empiric therapy in this setting.

Data developed previously at the University of Maryland indicated that imipenem has the spectrum and degree of antimicrobial activity required to provide adequate empiric therapy in febrile granulocytopenic cancer patients (4, 11, 12). Studies in volunteers which integrated the pharmacologic and microbiologic activity by measuring serum bactericidal activity and duration of time that serum concentrations remained above the MIC suggested that imipenem is a good candidate for study as monotherapy in the granulocytopenic host (11). Based on this preclinical evaluation, as well as evaluation of imipenem in a neutropenic animal model (8), a randomized, double-blinded, controlled trial of high-dose imipenem as a single antimicrobially active agent (1 g intravenously every 6 h) compared with a control regimen was initiated.

Frequently, the dosing schemes used in clinical trials are based on pharmacologic information drawn from volunteer populations. Information regarding drug disposition in target populations (such as febrile granulocytopenic cancer patients) is scarce and may differ from that for normal volunteers. Additionally, animal data suggest that for many beta-lactams maintaining concentrations in excess of inhibitory concentrations for the offending pathogen(s) may be critical for optimal therapeutic outcome (5, 10). Therefore, we believed it important to document early in this clinical trial the serum concentration-time profiles and pharmacokinetics of imipenem in our study population. The purpose of this communication is to present these data.

All patients studied were febrile (>100.4°F [38°C]) granulocytopenic (<1,000 polymorphonuclear leukocytes per μl) cancer patients with a serum creatinine of <1.5 mg/dl. Written informed consent was obtained according to institutional guidelines. Patients were randomized in a double-blinded fashion to receive either imipenem-cilastatin (1,000/1,000 mg intravenously every 6 h) plus placebo every 6 h or the control regimen (piperacillin-amikacin). Doses were dissolved in 200 ml of 5% glucose and water and administered intravenously over 30 to 45 min by a constant-infusion pump.

Pharmacokinetic sampling was performed with the antimicrobial therapy blinding intact. The antibiotic code was then revealed for the purposes of analysis of this study only for investigators who were not involved in the evaluation of efficacy and toxicity (G.L.D., K.I.P., A.F., and H.C.S.). Patients were studied during a steady-state-dosing interval. Samples of blood were obtained before drug administration, at the end of drug administration, and at 20 min, 45 min, and 1, 1.5, 2.5, 3.5, 4.5, and 5.5 h after termination of the infusion. Plasma was promptly separated in a refrigerated centrifuge (2 to 5°C) and, because the samples were collected in a double-blinded fashion, all samples were stabilized by the addition of an equal volume of a 1:1 mixture of 1 M morpholinoethanesulfonate buffer (pH 6.0) and ethylene glycol and then stored at −70°C until the time of assay.

Imipenem in plasma was assayed in our laboratory by the high-pressure liquid chromatographic technique described by Gravallese et al. (7). The plasma imipenem assay was linear over the range of 0.48 to 80 μg/ml; the interday coefficients of variation were 0.28% at 96.1 μg/ml, 5.2% at 53.8 μg/ml, and 4.7% at 2.6 μg/ml.

A model was fit to the plasma drug concentration data (one-, two-, or three-compartment open model with elimi-

TABLE 1. Demographic information on patients receiving imipenem-cilastatin (1,000/1,000 mg) every 6 h

Patient	Age (yr)	Sex[a]	Ht [in. (cm)]	Wt (kg)	CR[b] (mg/dl)	BSA[c] (m^2)
1	68	F	60.9 (155)	38.2	0.6	1.31
2	52	F	63.0 (160)	76.4	0.8	1.80
3	70	M	65.5 (166)	51.8	1.0	1.57
4	44	M	73.0 (185)	65.5	0.7	1.87
5	63	M	67.0 (170)	69.0	1.3	1.75
6	56	F	64.0 (163)	56.4	0.7	1.60

[a] M, Male, F, female.
[b] CR, Serum creatinine.
[c] BSA, Body surface area.

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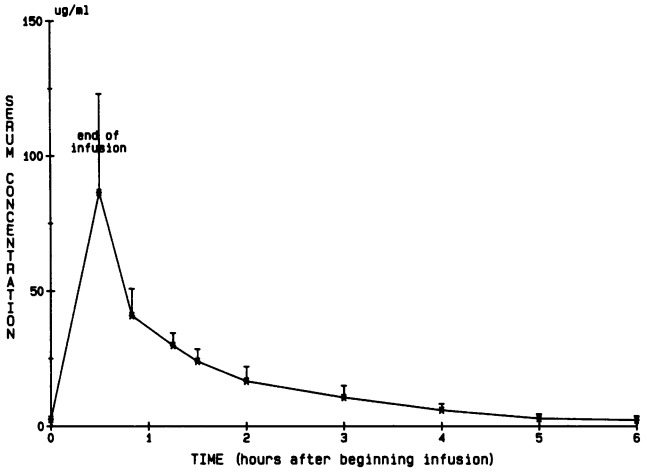

FIG. 1. Steady-state plasma concentration-time profile of imipenem after a 1,000/1,000-mg infusion of imipenem-cilastatin over 30 min (mean ± standard deviation).

nation from the central compartment) by an iterative, nonlinear, least-squares-weighted regression technique (2). The Nelder-Mead search algorithm and inverse variance of assay weighting were used. Choices between models were determined by using an F test. Derived pharmacokinetic parameters were calculated by standard methods (6). When different populations were compared, mean values of population pharmacokinetic parameters were examined for significance of differences by using an unpaired *t* test. Variances in the populations were compared by using an F test. An alpha value of ≤ 0.05 was deemed to be significant.

Characteristics of patients are shown in Table 1. The mean serum concentration-time profile at steady state for imipenem is shown in Fig. 1.

All six datum sets were best described by a linear two-compartment open model with elimination from the central compartment. Values for pharmacokinetic parameters are shown in Table 2.

If we wish to implement pharmacokinetically based dose-alteration schemes to optimize patient outcomes in high-risk groups, such as febrile granulocytopenic cancer patients, it is important to obtain information on disposition of antimicrobial agents in such target populations. The results of this study validate the importance of this, because the observed pharmacokinetics for imipenem were both different from and more variable than those observed in volunteer populations. The half-life was longer, clearance was lower, and volumes of distribution were larger than those seen in volunteer populations previously studied at this institution. All these changes are consistent with the greater age and the degree of illness demonstrated by the febrile granulocytopenic cancer patients we were treating.

These alterations in pharmacokinetics may be important. There is a growing body of literature which supports the maintenance of free drug concentrations in excess of the MIC for clinically important pathogens to optimize outcome when beta-lactam antibiotics are considered as the treatment agents (3, 5, 9, 10).

Escherichia coli, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and *Staphylococcus aureus* are the pathogens most frequently recovered from the blood of granulocytopenic cancer patients. Previous work at this institution documented protein binding for imipenem to be less than 13% (11). When the population average parameter values from our neutropenic patients and the protein-binding values referenced above are used to calculate free drug concentrations, imipenem remains above the MIC for 90% of *E. coli* (0.25 μg/ml), *K. pneumoniae* (0.5 μg/ml), *S. aureus* (0.03 μg/ml), and *P. aeruginosa* (4.0 μg/ml) strains for greater than 6 h for the first three pathogens and 4 h for *P. aeruginosa*. In Table 3, we present the amount of time on average that this dose of imipenem should achieve concentrations which remain above MICs, ranging from 8 to 1 μg/ml, in cancer patients, when calculated in the manner outlined above.

TABLE 3. Duration that free drug exceeds selected concentrations at steady state for an imipenem regimen of 1,000 mg every 6 h[a]

Concn (μg/ml)	Duration (h)
8	2.8
4	3.9
2	5.0
1	>6.0

[a] Concentrations in serum were simulated by using the population mean pharmacokinetic parameter values shown in Table 2.

TABLE 2. Pharmacokinetic parameter values of imipenem in febrile granulocytopenic cancer patients and normal volunteers[a]

Subjects	V_1 (liters/kg)	V_{ss} (liters/kg)	V_{area} (liters/kg)	CL (liters/h per 1.73 m²)	$t_{1/2\alpha}$ (h)	$t_{1/2\beta}$ (h)	AUC (mg · h/liter)
Granulocytopenic patients[b]							
1	0.15	0.31	0.35	10.6	0.11	1.15	124.7
2	0.09	0.20	0.26	8.3	0.18	1.57	115.6
3	0.18	0.38	0.46	10.7	0.19	1.70	102.6
4	0.26	0.33	0.34	13.6	0.14	1.06	68.0
5	0.16	0.27	0.59	8.2	0.66	3.38	119.7
6	0.06	0.08	0.12	8.6	0.17	0.59	125.6
Mean ± SD	0.15 ± 0.07	0.26 ± 0.10[c]	0.35 ± 0.16[c]	10.0[d] ± 2.1[c]	0.24 ± 0.21	1.57 ± 0.97[c]	109.4[d] ± 21.9[c]
Normal volunteers (n = 6)[e] (mean ± SD)	0.16 ± 0.05	0.23 ± 0.03	0.25 ± 0.04	12.1 ± 0.6	0.23 ± 0.12	0.93 ± 0.09	74.1 ± 6.4

[a] V_1, Volume of distribution in the central compartment; V_{ss}, volume of distribution at steady state; V_{area}, volume of distribution of drug in the body; CL, serum clearance; $t_{1/2\alpha}$, distributional half-life; $t_{1/2\beta}$, elimination half-life; AUC, area under the curve.

[b] Values were determined during a steady-state-dosing interval.

[c] Significantly more variable compared with normal volunteers; $P < 0.05$ (F test).

[d] Significantly different compared with normal volunteers; $P < 0.05$ (one-tailed).

[e] Reference 4.

These data can be adapted to other facilities if the MICs for the organisms in those facilities are known. Imipenem also possesses a postantibiotic effect against *P. aeruginosa* of approximately 2 h (1), and we have seen a 4-h time of free drug in excess of the MIC for 90% of the *P. aeruginosa* strains in our institution. Accordingly, we believe that the use of imipenem as single-agent empiric therapy in the granulocytopenic cancer patient population is reasonable. The validity of this conclusion is being tested in a large randomized, double-blinded, controlled evaluation.

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