Pharmacokinetics of Imipenem in Serum and Skin Window Fluid in Healthy Adults after Intramuscular or Intravenous Administration

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The pharmacokinetic profiles of imipenem after intramuscular (i.m.) and intravenous injections were examined in adult volunteers. Levels of imipenem in serum after i.m. injection of a microcrystalline suspension of imipenem-cilastatin (500 mg each) reached a peak (8.0 µg/ml) at 1.5 h after administration, and concentrations were maintained in excess of 1.5 µg/ml for 6 h. Serum elimination half-life (1.3 h), volume of distribution (14.5 liters), and area under the curve (AUC; 27.8 µg·h/ml) after i.m. injection did not significantly differ from those of a comparable dose given by intravenous infusion. Bioavailability after i.m. injection was 89%. Imipenem levels in skin window fluid after i.m. administration were maximal (4.3 µg/ml) at 4 h after injection, at which time imipenem concentrations exceeded those produced by intravenous infusion. The AUCskin window/AUCserum ratio for skin window fluid after i.m. injection was 68%, indicating good penetration of the drug into skin fluid. This study shows that i.m. injection of 500 mg of imipenem-cilastatin results in concentrations of imipenem in serum and skin fluid that are, for at least 6 h, consistent with antimicrobial activity against susceptible organisms.

Imipenem (N-formimidoyl thienamycin) is a carbapenem antibiotic with a wide spectrum of activity against aerobic and anaerobic gram-positive and gram-negative organisms. Imipenem is routinely combined with an equal amount of cilastatin, which blocks the renal biotransformation of imipenem, lessening its nephrotoxic potential while enhancing its recovery in urine. Pharmacokinetic analyses have been performed after single- and multiple-dose intravenous (i.v.) administration of imipenem in healthy adult volunteers (3, 4). Recently, preparations of imipenem-cilastatin suitable for intramuscular (i.m.) administration have become available for the treatment of susceptible organisms (5). In this report, we compare the pharmacokinetics of imipenem after i.m. and i.v. administration in healthy volunteers. Furthermore, since imipenem is often used in the treatment of skin infections, we have used the skin window fluid model (12) to study the distribution of imipenem to cutaneous interstitial fluid following administration by the two routes.

MATERIALS AND METHODS

Subjects. Human adult males ranging from 21 to 48 years of age whose body weights were within 10% of ideal were recruited for this study. Written informed consent was obtained from each volunteer according to institutional guidelines, and the study was approved by the Akron City Hospital Research Committee. Physical examination, complete blood counts, urinalysis, and blood chemistry studies (including electrolytes and liver and renal function tests) were all within normal limits.

Drug. The drug was supplied by Merck Sharp & Dohme Research Laboratories (Rahway, N.J.) in vials containing 500 mg of imipenem and 500 mg of cilastatin. In the first two experiments, imipenem plus cilastatin (1:1) was given via an indwelling heparin lock in a forearm vein at a dose of either 500 or 1,000 mg in 100 ml of sterile saline delivered over a 30-min period by a constant-delivery infusion pump. This method of infusion was chosen because it closely resembled the protocol followed in a clinical setting. In the third experiment, a microcrystalline suspension of imipenem with cilastatin (500 mg each) was given as a single i.m. injection in a buttock. Ten volunteers received the 1,000 mg i.v. dose. Eight of these returned to participate in the 500-mg i.m. testing, while four returned to receive the 500 mg i.v. dose. The testing periods were separated by drug-free intervals of 7 days.

Sampling of body fluids. Whole blood was obtained from the antecubital vein on the side of the body opposite that used for i.m. injection or i.v. infusion. Blood samples were collected at 0, 0.5, 1, 1.5, 2, 3, 4, 5, and 6 h after the onset of drug administration. Blood was collected in sterile glass tubes and allowed to clot, and serum was promptly separated from blood cells by centrifugation at 1,400 × g. Within 1 h of collection, all specimens were mixed with an equal volume of stabilizing buffer (1 part 1 M morpholineethane sulfonate buffer, pH 6, and 1 part ethylene glycol) and stored at −70°C until assay. Cutaneous-tissue fluid was obtained by using the skin window technique previously described by Tan et al. (12) with modifications. In brief, a small area (approximately 1 cm²) of skin on the medial forearm was cleansed with ethyl alcohol, and the epidermis was removed by scraping with a scalpel blade. The exposed wound was covered with a sterile stainless-steel chamber fitted with a self-sealing rubber septum. One hour prior to administration of drug, 1 ml of sterile isotonic saline was injected into the chamber. Thereafter, approximately 0.1 ml of skin window fluid was removed from the skin window chamber to assay imipenem at each sampling period (0, 0.5, 1, 1.5, 2, 3, 4, 5, and 6 h).

Drug measurement. Imipenem concentrations in serum and skin window fluid were analyzed by the well agar diffusion technique described by Bennett et al. (1). A spore
suspension of the indicator organism *Bacillus subtilis* (Difco Laboratories, Detroit, Mich.) was used to inoculate the bacterial lawn used for the assay. Drug-free serum was used as a diluent for known standard concentrations (20, 10, 5, 2.5, 1.25, and 0.625 μg/ml) when serum was assayed. The interassay and intraassay coefficients of variation for these imipenem standards in serum ranged from 4.2 to 7.5 and 1.2 to 2.8%, respectively. Experimental serum samples which exceeded 20 μg of imipenem per ml were diluted 1:10 with drug-free serum, and samples which fell below the lowest imipenem standard were extrapolated along the linear regression standard curve. Phosphate-buffered saline (0.1 M, pH 6) was used as a diluent for standards and skin fluid specimens. The interassay and intraassay coefficients of variation for the buffered-saline-diluted standards (as described above for serum) ranged from 5.2 to 8 and 1.2 to 1.9%, respectively. All experimental samples were tested in four replicates. The lowest reproducible estimated imipenem concentration recorded for each specimen was 0.2 μg/ml.

**Kinetic analysis.** Pharmacokinetic parameters of the serum and skin window fluid imipenem concentration-time curves were derived from an analysis of the mean values for individual volunteers. Semilogarithmic transformation of the serum imipenem elimination data was analyzed by using one- and two-compartment modeling (7). In both cases, elimination rate constants (8) were obtained from least-squares regression curve fitting of the terminal portion of the plot (11). In the case of data for i.m. administration of drug, time points at 4, 5, and 6 h were used for this estimation to avoid curve bias due to the drug absorption phase. Elimination half-life (t1/2β) and apparent volume of distribution (V = dose/C0, where C0 is the time zero intercept of the plot of back-extrapolated concentration in serum versus time) were estimated by assuming single-compartment models. Trapezoidal rule integration of the area under the curve (AUC) for plots of imipenem concentrations in serum and skin window fluid versus time was calculated over the 6-h sampling period (11). Bioavailability (f = AUCi.m./AUCi.v., AUCi.m. was calculated by using the largest sample groups (1,000 mg i.v. and 500 mg i.m.). Percent penetration of imipenem into skin window fluid was calculated as (AUCskin window/AUCserum) × 100 for each route of administration. Results are expressed as mean ± standard deviation, and where appropriate, statistical evaluations were performed by using analysis of variance (11).

**RESULTS**

Administration of imipenem-cilastatin i.v. and i.m. was generally well tolerated by the volunteers; however, three subjects (two after 1,000 mg i.v. and one after 500 mg i.v.) experienced epigastric discomfort, diaphoresis, and/or orthostatic hypotension. Ten subjects received a 30-min constant i.v. infusion of 1,000 g each of imipenem and cilastatin, and a semilog transformation of the curve for concentration of imipenem in serum versus time was characterized by a combined distribution-elimination phase during the first 2 h after initiation of infusion followed by a reduction in the slope of the curve connecting time points from 2 to 6 h (elimination phase) (Fig. 1). The peak concentration of imipenem in serum (65.1 ± 12.4 μg/ml [mean ± standard deviation]) was observed upon termination of the infusion (0.5 h). Other pharmacokinetic parameters presented in Table 1 include t1/2β (1 h), V (21.2 ± 2.9 liters), and AUC (63.9 ± 9.1 μg·h/ml).

The monophasic log plot of concentration in serum versus time resulting from a 500-mg 30-min i.v. infusion was more adequately described by using single-compartment modeling (Fig. 1). Upon completion of infusion (i.e., at 0.5 h), the average concentration of imipenem in serum peaked at 19.3 ± 3.3 μg/ml. The imipenem t1/2β for a 500-mg dose also approached 1 h, and the integrated AUC (22.1 ± 5.5) was distributed through 22.8 ± 5.9 liters (Table 1).

Administration i.m. of 500 mg of imipenem-cilastatin resulted in 89% imipenem bioavailability. The plot of i.m. imipenem concentration in serum versus time rose slowly to a peak (8.0 ± 2.7 μg/ml) at 1.5 h after injection. The serum t1/2β (1.3 ± 0.4) was slightly elevated, the V (14.3 ± 12.2) was lower, and the AUC (27.8 ± 6.7) was higher than with the i.v. route. No statistically significant differences in AUC or t1/2β were detected for identical doses administered via the i.m. and i.v. routes.

Imipenem in skin window fluid reached a peak concentration of 14.9 ± 3.8 μg/ml at 2 h after the onset of a 1,000-mg imipenem infusion (Fig. 2). The curve for imipenem concentrations in skin window fluid versus time for the 500-mg i.v. dose was similar to that produced by the higher dose, though achieving proportionally lower peak levels in skin window fluid (8.6 ± 1.3 μg/ml) at 1.5 h. In comparison with i.v. dosing, a 500-mg i.m. dose of imipenem resulted in peak levels of imipenem in skin window fluid (4.3 ± 2.2 μg/ml) at 4 h postinjection (Fig. 2). Although the mean levels of imipenem in skin window fluid resulting from i.m. administration exceeded those resulting from i.v. administration during 3 to 6 following injection, the 1,000-mg i.v. i.dose surpassed levels produced by the 500-mg injection at all times tested (Fig. 2). Percent penetration of imipenem into skin window fluid was quite variable, ranging from 28 to 143% over the three doses (Table 1). There was no statistically significant difference between the mean percent penetration values for 500 mg i.m. (68%), 500 mg i.v. (118%), or 1,000 mg i.v. (76%).
The pharmacokinetics of imipenem in serum and skin window fluid were studied after i.v. and i.m. injection of imipenem-cilastatin. The study was performed in a nonrandomized block design that under some circumstances could result in sequence bias. Volunteers in this study received imipenem-cilastatin on three occasions, differing by dose or route, separated by 1-week drug-free intervals. There was no evidence that this particular design resulted in significant bias.

In serum, the $t_{1/2b}$ AUC, and $V'$ of imipenem after a 30-min constant i.v. infusion were similar to what has previously been reported for healthy adults (3, 4). The i.m. route, however, resulted in a curve for concentration of imipenem in serum versus time that was slower to reach a peak than the curve for the i.v. route yet maintained imipenem levels in excess of those resulting from a 500-mg i.v. dose for nearly 5 h postinjection and greater than those observed following a 1,000-mg i.v. dose for at least 3 h. This phenomenon can be explained by the fact that the imipenem-cilastatin i.m. dose is injected as a microcrystalline suspension. As the dose gradually dissolves, imipenem is constantly being released into the blood stream, maintaining imipenem levels more constant over time than those resulting from i.v. administration. The prolonged release of imipenem from the i.m. depot tends to distort the curve for concentration in serum versus time, resulting in a shallower elimination slope and a reported increase (from 1 h i.v. to 2.5 h i.m.) in the apparent $t_{1/2}$ of the drug (6). On the other hand, using the most terminal points (h 4 to 6) of the concentration-versus-time curve, we have calculated the serum $t_{1/2}$ for imipenem after i.m. injection to be 1.3 h. The basis for this discrepancy is not clear. Nevertheless, peak concentration in serum (8.0 µg/ml) and bioavailability (89%) after a 500-mg i.m. dose were similar to what has previously been reported (6).

Imipenem concentrations in skin window fluid peaked within 1.5 to 2.0 h after i.v. dosing. Although the peak concentration in skin window fluid (8 µg/ml) was similar to those reported for an identical dose in humans when the cantharides-induced blister fluid technique was used (7 µg/ml) (13), imipenem appears not to distribute as rapidly to skin window fluid as it does to inflammatory fluid. The slower distribution of antibiotic into the skin window fluid may have resulted from between-volunteer variation in the skin surface area prepared for the sampling chamber as well as from variations in the depth and uniformity of epidermis removal. This may also explain the high degree of variability that was observed in the percent penetration data for skin window fluid.

Injection i.m. resulted in imipenem levels in skin window fluid that, like those in serum, were delayed in reaching a peak concentration that was on the average lower than those achieved by the i.v. route. However, the i.m. depot did maintain levels in skin window fluid between 3 and 5 µg/ml for over 4 h postinjection, with an estimated 68% of the AUC for serum penetrating the cutaneous fluid, which corresponds well with the 68% penetration of imipenem into cantharides-induced skin blister fluid after i.v. administration, as reported by Wise et al. (13). These data indicate that imipenem penetrates skin tissue fluid well compared with other beta-lactam antibiotics such as carbenicillin, cefotaxime, ceftriaxone, or flucloxicillin (13).

Concentrations of antibiotics in serum and skin window fluid can be used to predict therapeutic efficacy for systemic and localized skin infections. Table 2 shows that an i.m. injection of 500 mg of imipenem resulted in antibiotic levels in serum that exceeded the MIC for 90% for strains (MIC$_{90}$) of highly susceptible organisms (MIC$_{90}$ up to 6.0 µg/ml) for as long as or longer than those resulting from either i.v. dose. This analysis suggests that for systemic infections due to highly susceptible organisms, i.m. administration of 500 mg of imipenem-cilastatin may be equally or more efficacious than a higher dose given by the i.v. route.

Levels of imipenem in skin window fluid after i.m. dosing exceeded the MIC$_{90}$s for highly and moderately susceptible organisms for less time than imipenem given i.v. In fact, after i.m. dosing, imipenem in skin window fluid did not
reach levels commensurate with eradication of more resistant organisms. Higher imipenem levels in skin window fluid after i.v. infusion were most likely due to a greater driving force for diffusion.

The results of this study support the use of i.m. imipenem preparations in lieu of i.v. administration for susceptible organisms and when the i.m. route is appropriate for the clinical setting. For all but the most resistant organisms, a 500-mg i.m. dose of imipenem results in imipenem concentrations in serum and skin tissue fluid in excess of the MIC90 for susceptible organisms for more than 6 h after injection. Even as the levels of imipenem in serum or cutaneous tissue fluid fall below the MIC90 for a susceptible organism (i.e., between twice-daily doses), the levels would be maintained for sufficient time to facilitate the postantibiotic effect for a number of common pathogens (Pseudomonas aeruginosa, Escherichia coli, Staphylococcus aureus) (2, 8). Indeed, clinical studies which show excellent eradication of both systemic and soft tissue (skin) infections by use of i.m. injections (500 mg of imipenem-cilastatin every 12 h) (5, 9) support our claims. On the basis of this information, i.m. preparations of imipenem-cilastatin should be more frequently considered for the treatment of susceptible systemic and skin infections.

ACKNOWLEDGMENT

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REFERENCES


TABLE 2. Dwell time of average imipenem concentrations in sera or skin window fluids of human volunteers

<table>
<thead>
<tr>
<th>Dose (mg) and route of administration</th>
<th>Highly susceptible</th>
<th>Moderately susceptible</th>
<th>Mildly susceptible</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Serum</td>
<td>Skin window</td>
<td>Serum</td>
</tr>
<tr>
<td>500 i.m.</td>
<td>0.5-6.0</td>
<td>1.2-6.0</td>
<td>0.5-5.0</td>
</tr>
<tr>
<td>500 i.v.</td>
<td>0.5-3.7</td>
<td>0.5-5.4</td>
<td>0.5-2.8</td>
</tr>
<tr>
<td>1,000 i.v.</td>
<td>0.5-5.3</td>
<td>0.5-6.0</td>
<td>0.5-4.0</td>
</tr>
</tbody>
</table>

* Dwell time is the number of hours after initiation of treatment that concentration of drug exceeded the mean MIC90 of selected organisms. Susceptibility data were derived from geometric mean MIC90 compiled by Shungu (10).
φ Drugs administered were imipenem and cilastatin.
‡ Bacteroides fragilis, Campylobacter fetus spp., Clostridium perfringens, Enterobacter aerogenes, E. coli, Klebsiella pneumoniae, Listeria monocytogenes, Neisseria gonorrhoeae, peptococci, peptostreptococci, Salmonella spp., Shigella spp., Staphylococcus aureus, Staphylococcus epidermidis, Streptococcus pyogenes, Streptococcus viridans group. MIC90 < 1.5 µg/ml.
§ Fusobacterium spp., Haemophilus influenzae, Providencia stuartii, Serratia marcescens, S. aureus (methicillin resistant), Streptococcus faecalis. MIC90 = 1.5 to 3.0 µg/ml.
¶ Clostridium difficile, Morganella morganii, Proteus mirabilis, Proteus vulgaris, P. aeruginosa. MIC90 ≤ 6.0 µg/ml.
† NC, no coverage (antibiotic levels never exceed the mean MIC90 for those selected organisms).