Imipenem/Cilastatin: Rationale for a Fixed Combination

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Imipenem is renally metabolized to the stable open-lactam metabolite by a dipeptidase, dehydropeptidase I, located at the luminal surface of the proximal tubular cells. In humans the degree of hydrolysis shows marked intersubject variability but minimal intrasubject variability. In healthy subjects the urinary recovery of unchanged imipenem ranged from 5.5% to 42.5% of the dose. Cilastatin inhibits the metabolism of imipenem and increases the urinary recovery of active imipenem to about 70% of the dose when a combination of imipenem and cilastatin in a 1:1 ratio is used. In healthy volunteers, the pharmacokinetics of imipenem and cilastatin are similar, but in patients with renal impairment, cilastatin is eliminated more slowly than imipenem. Both compounds have a high degree of safety. However, very high doses of imipenem induce tubular toxicity in rabbits. That effect can be blocked by using a combination of imipenem and cilastatin. The use of a fixed combination of imipenem and cilastatin is motivated by the increases in urinary recovery of imipenem with the combination and by the elimination of the nephrotoxic potential associated with the administration of imipenem alone.

Metabolism of Imipenem

Animal Studies

Pharmacokinetic studies in various animal species demonstrated that high serum concentrations of imipenem could be achieved but that the recovery of active imipenem from urine, though levels varied among species, remained consistently below 60% of the dose administered [5]. By comparing plasma clearance of imipenem in normal animals with that in animals in which the renal artery had been ligated, investigators showed that a majority of the drug was eliminated via the kidneys (table 1), a finding that supported the assumption that the drug is metabolized in the kidneys. With thienamycin, which showed a similar pharmacokinetic pattern, it could be demonstrated that kidney homogenates from mice, rats, pigs, and humans inactivated the antibiotic, whereas liver homogenates had no such effect [5]. The inactivating factor was heat-labile and could be eliminated by treatment of the homogenate with EDTA. Purification of kidney homogenate made it possible to isolate an enzyme that could be identified as dehydropeptidase I (DHP-I), which had previously been described by Greenstein [7]. DHP-I had been shown to hydrolyze several synthetic dehydrodipeptides as well as naturally occurring dipeptides. Because of the striking structural similarity between these substances and imipenem (figure 1), it was suggested that DHP-I acts by breaking the β-lactam bond in the imipenem molecule. Support for...
Table 1. Urinary recovery, plasma half-life, and plasma clearance of imipenem in three animal species.

<table>
<thead>
<tr>
<th>Animal species</th>
<th>Treatment</th>
<th>Urinary recovery ( % of dose)</th>
<th>Plasma half-life (min)</th>
<th>Plasma clearance (ml/min/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rabbit</td>
<td>None</td>
<td>44</td>
<td>16</td>
<td>33.0</td>
</tr>
<tr>
<td></td>
<td>Nephrectomy</td>
<td>...</td>
<td>86.0</td>
<td>1.4</td>
</tr>
<tr>
<td>Dog</td>
<td>None</td>
<td>8</td>
<td>31</td>
<td>6.2</td>
</tr>
<tr>
<td>Chimpanzee</td>
<td>None</td>
<td>14</td>
<td>45</td>
<td>4.4</td>
</tr>
</tbody>
</table>

NOTE. Data are from [6].

that hypothesis was provided by the demonstration of loss of ultraviolet absorbance at 230 nm by a solution of imipenem exposed to DHP-I in vitro [5]. Further proofs were obtained by demonstration by high-performance liquid chromatography (HPLC) of the identity of both an in vivo metabolite of imipenem and the principal product of hydrolysis of imipenem by DHP-I.

Indications emerged, therefore, that despite its high degree of resistance to bacterial β-lactamases, imipenem is highly susceptible to a mammalian β-lactamase that is inactive against the penicillins and cephalosporins but that, to various degrees, hydrolyzes all carbapenem antibiotics so far studied [5]. DHP-I has been localized to the luminal face—the brush border—of the proximal tubular cells of the kidney [8]. It has access both to imipenem in glomerular filtrate and to imipenem excreted by tubular secretion. DHP-I has, however, relatively low affinity for imipenem; the hydrolysis of imipenem by DPH-I is only 0.85% that of the natural substrate, the dehydropetode [5].

Metabolism in Humans

The metabolism of imipenem by DHP-I was shown to be more pronounced in humans than in animals. Whereas the degrees of metabolism in various individuals of the same animal species were similar, among healthy human subjects the degree of variation was wide [9, 10] (figure 2). The percentage of the dose recovered in these subjects ranged from 5.5% to 42.5%, and the degree of metabolism was independent of the dose of imipenem administered. In the individual subjects, only small variations in urinary recovery were found, even when up to three years had elapsed between the imipenem doses (table 2). Studies of four healthy subjects administered radiolabeled imipenem showed that almost 100% of the radioactivity could be recovered from urine within 96 hr, the greater part being excreted within 10 hr [11]. HPLC of the urine of one subject for whom the rate of urinary recovery of active imipenem was 12% demonstrated that 80%–90% of the radioactivity represented the open-lactam metabolite of imipenem, a finding that strongly supports the mechanism for metabolism of imipenem by DHP-I discussed above. A practical consequence of the renal metabolism of imipenem is that when drug is administered alone, urinary concentrations >10 μg/ml—i.e., the concentrations corresponding to the MIC for the less susceptible strains of *P. aeruginosa*—can be maintained only for ~4 hr after administration of a 250-mg dose and for ~6 hr after administration of a 500-mg dose [9].

Cilastatin

Since individuals whose rate of renal metabolism of imipenem is high would require high doses of imipenem if infections in the urinary tract were to be treated with imipenem alone, a search for an inhibitor of DHP-I was instituted. The result was the development of a series of 2.2(+)-dimethylcyclopro-
pilocarcin-2-amino-3-alkyl-(Z)-propenoates [12]. These compounds competitively and reversibly inhibit DHP-I but do not react with other mammalian enzymes, such as angiotensin-converting enzyme from rat lung. Considering the pharmacokinetic properties of imipenem in the chimpanzee, investigators selected two compounds for further study, MK0789 and cilastatin (MK0791), both of which have a disposition in the chimpanzee similar to that of imipenem and lack toxicity in animals, even at high doses. Both are capable of inhibiting the metabolism of imipenem for longer than many of the other derivatives studied [6]. They lack antibacterial effect even in very high concentrations. Ultimately, cilastatin was chosen as the most suitable compound for combining with imipenem.

**Effect of Cilastatin on Potential Nephrotoxicity of Imipenem**

Doses of imipenem >100 mg/kg induced acute tubular necrosis in the rabbit [6]. When cilastatin and imipenem were coadministered at doses of up to 360 mg/kg of each component, no nephrotoxicity could be detected. It was proposed that the mechanism by which cilastatin protects the kidneys is by preventing accumulation of imipenem and/or its metabolites in the tubular cells. It is then more probable that the metabolites would be accumulated due to the rapid metabolism of imipenem by DHP-I in the absence of DHP-I inhibitors. Support for that theory was provided by studies of the concentrations in the kidney cortex of imipenem, its open-lactam metabolite, and cysteine-conjugated imipenem after the administration of imipenem alone or together with a DHP-I inhibitor. Two hours after administration of 142 mg of imipenem/kg to a rabbit, the concentrations in the kidney cortex were 60 μg of imipenem/g, 1,200 μg of the open-lactam metabolite/g, and 1,060 μg of the cysteine-conjugated imipenem/g. Following the administration of a dose of 128 mg of imipenem/kg plus 90 mg of a DHP-I inhibitor/kg (MK0789), the corresponding concentrations were 8, 160, and 570 μg/g, respectively. However, it is still not clear which of these three compounds is responsible for the nephrotoxic potential of imipenem in experimental animals.

**Effects of Cilastatin on the Disposition of Imipenem**

In humans, the most striking effect of cilastatin when combined with imipenem is the increase in urinary recovery of active imipenem to ~70% of the dose, irrespective of the degree of metabolism of imipenem when administered alone [13]. Evidence for an inhibition of DHP-I by cilastatin was provided by the data for the subject mentioned above who received radiolabeled imipenem. When cilastatin was coadministered, the open-lactam metabolite of imipenem accounted for ~20% of the radioactivity in the urine during the first hour after administration and ~55% during the fourth to sixth hour [11]. As a consequence of the reduced metabolism of imipenem, urine concentrations of ≥10 μg/ml were maintained for at least 8 hr after administration of a dose of 500 mg of imipenem and 500 mg of cilastatin [13].

The effects of cilastatin on the systemic disposition of imipenem were less striking. As reviewed by Rogers [14], coadministration of the two drugs results in a very slight increase of the half-life of imipenem in plasma, an increase of ~20% of the area under the plasma concentration-time curve, and a corre-
responding decrease in the plasma clearance of imipenem. Kahan et al. [6] have postulated that in the absence of a DHP-I inhibitor about one-third of the renally cleared imipenem enters the proximal tubular cells through the contraluminal surface of the cells. Since about two-thirds of the fraction that is filtered will be subject to rapid DHP-I metabolism the concentration of intact imipenem in the tubular lumen is likely to be lower than that in the plasma. The influx of imipenem into the tubular cell can then take place through passive diffusion. Probenecid, which blocks anionic active transport at the contraluminal surface, will lack effect, a finding that was nicely demonstrated in chimpanzees. However, when cilastatin is coadministered with imipenem, the plasma concentration of imipenem is lower than the tubular concentration and entry of imipenem into the tubular cell would require active transport. It follows that probenecid markedly reduces the renal clearance of imipenem without noticeably affecting the total recovery of imipenem in the urine of chimpanzees. This net tubular secretion of imipenem in the presence of DHP-I inhibitors was found to be present until the plasma levels of the inhibitor declined to a point at which intratubular degradation of imipenem could no longer be suppressed. At that point the plasma clearance increased to the value for imipenem alone. This mechanism seems fully applicable to the analysis of results of studies with human subjects and would explain the changing renal and plasma clearance of imipenem at various times after administration [13].

In the studies of imipenem and cilastatin in healthy subjects, various ratios between the two components have been used. At ratios of imipenem to cilastatin of 1:0.25, 1:0.5, 1:1, and 1:2, similar total recoveries of active imipenem from urine were found [13]. However, if incremental recoveries were studied, it could be demonstrated that the higher the relative dose of cilastatin, the more prolonged the inhibition of imipenem metabolism. Optimal inhibition during a dose interval of up to 10 hr could be obtained when the ratio between imipenem and cilastatin was 1:1. If a further 15% increase in the urinary recovery of imipenem was obtained by doubling the dose of cilastatin—to give a ratio of 1:2—such a combination would lead to a risk of unnecessary accumulation of cilastatin in patients with reduced renal function. Verpoorten et al. [15] demonstrated that the plasma half-life of imipenem increased to ~3 hr in patients with severe renal impairment, while the corresponding figure for cilastatin was 12 hr. It can be assumed that the difference is due to the fact that ~25% of imipenem undergoes systemic metabolism, probably by nonspecific hydrolysis of the molecule to the open-lactam metabolite, whereas almost 90% of cilastatin is excreted in the urine as unchanged cilastatin (about 76%) or as its N-acetyl metabolite [11].

Clinical Rationale for the Imipenem/Cilastatin Combination

Published controlled clinical studies [16–19] have demonstrated that imipenem/cilastatin is at least as effective as cefazolin, cefotaxime, or moxalactam and more effective than a combination of gentamicin and clindamycin in the treatment of serious systemic infections. The frequencies of adverse reactions to imipenem/cilastatin in these and other studies [20] have been low; in one study [19] significantly lower frequencies of adverse reactions were reported for imipenem/cilastatin than for a combination of gentamicin and clindamycin. It is significant that the adverse reactions in patients who have received imipenem/cilastatin have been those normally seen in some patients receiving ß-lactam antibiotics. There have been no reports of adverse reactions attributed to cilastatin, a finding confirming the high degree of safety of that compound determined in toxicologic studies in animals (Merck & Co., data on file). The lack of adverse reactions related to cilastatin is reflected in the finding that in 49 healthy male subjects included in our phase-I studies who altogether received 305 iv doses of imipenem and/or cilastatin, the only adverse clinical reaction noted was one case of nausea related to rapid infusion of imipenem.

It can be argued that coadministration of cilastatin with imipenem is justified when infections localized in or originating from the urinary tract are treated but that the cilastatin component does not fill any function in other types of infections. This argument cannot be refuted because all studies so far performed as well as those underway have used the combination. However, several factors speak in favor of the combination over imipenem alone. If the antibiotic were to be available both as a single entity and in combination with cilastatin, distinguishing between the two in practice might be difficult. It is also often impossible to determine whether or not a serious systemic infection originates from the urinary tract. In the studies published so far, 20%
of all infections originated from the urinary tract, although none of the studies were designed to include patients with such infections specifically. A third factor in favor of the combination is that, whereas cilastatin does not seem to add any significant toxicity, there is evidence that it may reduce the potential risks of nephrotoxicity, which have been noted in rabbits treated with imipenem alone. Since in the rabbit the risk of nephrotoxicity with imipenem is equal—per weight unit—to that with cephaloridine, it seems ethically dubious to omit cilastatin. Finally, the imipenem/cilastatin combination bears striking similarities to the widely accepted combination of levodopa and carbidopa. In both cases an active substance is combined with an inhibitor of a uniformly present enzyme, which if not inhibited reduces the activity of the active substance.

References