The Pharmacology of Meropenem, A New Carbapenem Antibiotic

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Meropenem, a new β-lactam antibiotic, is more active against gram-negative bacilli and less active against gram-positive cocci than is imipenem, and there are several important structural differences between meropenem and the older carbapenems. These differences may be responsible for the lower potential for the induction of epileptogenic activity observed with meropenem as well as for its increased stability to degradation by dehydropeptidase-I. The pharmacokinetics of meropenem are typical of those of a parenteral β-lactam antibiotic with low protein binding and predominantly renal excretion. Dosage reduction is required for patients with reduced renal function; no dosage adjustment is required for patients with hepatic impairment. Meropenem has excellent penetration in abdominal tissues, bile, blister fluid, inflammatory exudate, cerebrospinal fluid (in the presence of inflammation), gynecologic tissues, respiratory tract tissues, and urinary tract tissues; tissue levels are generally equal to or above the levels needed for the treatment of patients with susceptible pathogens.

Structure-Activity Relationships

The carbapenem antibiotics are produced by substituting carbon for sulfur at position 1 and an unsaturated bond between carbons 2 and 3 of the familiar penicillin nucleus (figure 1). The carbapenem thienamycin was first discovered as a naturally occurring product of the soil microbe Streptomyces cattleya [4, 5]. Meropenem and imipenem, which are synthetic derivatives of thienamycin, contain a 6-hydroxyethyl side chain in which the hydrogens at carbons 5 and 6 are in a trans orientation with respect to each other, whereas classic penicillins and cephalosporins have side chains with a cis orientation at these positions. It is the trans orientation of the 6-hydroxyethyl moiety that is thought to confer the stability of carbapenems to degradation by a wide variety of β-lactamases. This stability is largely responsible for the high activity of the carbapenems against gram-negative bacteria [1, 6].

Meropenem differs in structure from imipenem by having a methyl group at the C1 position. The resistance of meropenem to degradation by DHP-I is thought to be mediated by this methyl group [7, 8]. Meropenem also has a unique side chain at C2 that contributes to enhanced activity against gram-negative organisms [1, 9]. This difference in side chains at the C2 position may account for the fact that meropenem has lower epileptogenic activity than does imipenem.

When administered into the cerebral ventricles or the subarachnoid space or directly into the cerebral cortex, many β-lactam antibiotics promote convulsions in animal models [2, 3, 10, 11]. The β-lactam ring itself is thought to be responsible for such activity, with modifications of the ring affecting the potential of the compound to induce seizures. The precise mechanisms are not understood, but it has been postulated that the convulsant properties of β-lactam antibiotics may be related either to antagonism of the γ-aminobutyric acid system or to accumulation of a metabolite [2, 3, 11].

In a recent study, 24 β-lactam antibiotics were administered via intracerebroventricular microinjection to rats, and the epileptogenic potentials of these compounds were measured and compared [3]. Among the cephalosporins studied, cefazolin had the most potent convulsant properties, while cefonicid, cefixime, cefuroxime, and cephradine did not demonstrate clear convulsant activity. Cefazolin, a cephalosporin with a tetrazole ring at position 7, has a structure similar to pentylenetetrazol, a convulsant agent. Benzylpenicillin was the most potent convulsant among the penicillins, although it was 2–4 times less potent than cefazolin.

The activity of imipenem was similar to that of benzylpenicillin and was four times greater than that of meropenem [3].
In mice, imipenem and imipenem/cilastatin (200 mg/kg iv) significantly potentiated the percentage of mice exhibiting metrazole-induced convulsions ($P < .05$). In the same model, however, meropenem failed to potentiate seizures when it was given in iv doses of 50–400 mg/kg [2]. Hori and colleagues [11] observed in an animal model that meropenem had weak convulsant activity as well as weak inhibition of γ-aminobutyric acid receptor binding in comparison with imipenem as well as with other β-lactams.

**Bacteriologic Activity**

Bacteriologic studies have confirmed that the activity of meropenem is similar to that of imipenem, which has the broadest antibacterial spectrum of any β-lactam agent available to date (table 1) [6, 12]. Meropenem is more active than imipenem against gram-negative aerobes, including those in the Enterobacteriaceae family, *Pseudomonas aeruginosa*, *Haemophilus influenzae*, and *Neisseria gonorrhoeae*. However, meropenem is less active than imipenem against staphylococci [12–15]. The drug is also considered to be less active than imipenem against *Clostridium* species [13]. The two compounds have approximately equivalent activity against streptococci and anaerobes such as *Bacteroides fragilis* [12, 16].

**Pharmacokinetics**

Like imipenem, meropenem is not orally absorbed. After being administered by the iv route, meropenem displays biexponential pharmacokinetics, with a rapid distribution phase preceding a terminal elimination phase with a half-life ($t_{1/2}$) of ~1 hour in patients with normal renal function. The mean plasma concentrations over time following a 5- and 30-minute iv infusion of 500 mg of meropenem in healthy volunteers is shown in figure 2 (data on file, Zeneca Pharmaceuticals). Terminal $t_{1/2}$ values rise slightly with increasing doses of meropenem, ranging from 0.94 hour to 1.11 hours over a dose range of 250 mg to 2 g.

Administration of meropenem via im injection is followed by an absorption phase, with a peak concentration between 10 minutes and 2 hours after dosing. The im route is also associated with a slightly longer $t_{1/2}$ and with peak concentrations that are approximately one-fifth the values attained by iv bolus and one-half those achieved by a 30-minute infusion (figure 2). The im route is considered bioequivalent to iv administration, with the mean (±SD) bioavailability of im meropenem being 93.8% ± 8.2% (data on file, Zeneca Pharmaceuticals).

Meropenem is widely distributed in humans, with a volume of distribution ($V_d$) at steady state on the order of 15–20 L [17–20] (data on file, Zeneca Pharmaceuticals). Only 2% of the drug is bound to serum proteins [17] (data on file, Zeneca Pharmaceuticals). A summary of pharmacokinetic data for meropenem in healthy volunteers is found in table 2 [5, 18, 19, 21–24].

ICI 213,689 is the only metabolite of meropenem and is produced by hydrolysis of the β-lactam bond, rendering the metabolite bacteriologically inactive. Typical plasma profiles of meropenem and its inactive open β-lactam ring metabolite (ICI 213,689) as a function of time are presented in figures 3 and 4 [17] (data on file, Zeneca Pharmaceuticals). ICI 213,689 has a longer apparent elimination $t_{1/2}$ (1.8–2.8 hours) than the parent compound (data on file, Zeneca Pharmaceuticals). Area-under-the-curve (AUC) values for the metabolite are ~10% of those for meropenem, so exposure to the circulating metabolite is low in patients with normal renal function. Exposure is about 50% greater after im injection than after iv administration because some presystemic conversion of meropenem to the open β-lactam ring metabolite is presumed to occur at the injection site.

In volunteers, ~60%–80% of an iv meropenem dose is recovered in urine as the parent compound (table 2) and...
Table 1. In vitro activities of meropenem vs. imipenem.

<table>
<thead>
<tr>
<th>Organism (no. of isolates)</th>
<th>Meropenem (MIC₉₀ mg/L)</th>
<th>Imipenem</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gram negative</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Escherichia coli</em> (50)</td>
<td>0.03 0.25</td>
<td></td>
</tr>
<tr>
<td><em>Klebsiella species</em> (32)</td>
<td>0.06 0.5</td>
<td></td>
</tr>
<tr>
<td><em>Serratia marcescens</em> (32)</td>
<td>0.25 1</td>
<td></td>
</tr>
<tr>
<td><em>Enterobacter aerogenes</em> (31)</td>
<td>0.06 2</td>
<td></td>
</tr>
<tr>
<td><em>Proteus mirabilis</em> (31)</td>
<td>0.12 4</td>
<td></td>
</tr>
<tr>
<td><em>Pseudomonas aeruginosa</em> <strong>(55)</strong></td>
<td>2 2</td>
<td></td>
</tr>
<tr>
<td><em>Acinetobacter anitratus</em> (30)</td>
<td>1 0.25</td>
<td></td>
</tr>
<tr>
<td><strong>Haemophilus influenzae</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>β-lactamase negative (26)</td>
<td>0.06 0.5</td>
<td></td>
</tr>
<tr>
<td>β-lactamase positive (21)</td>
<td>0.03 0.25</td>
<td></td>
</tr>
<tr>
<td>β-lactamase negative, ampicillin-resistant (11)</td>
<td>0.5 1</td>
<td></td>
</tr>
<tr>
<td><strong>Gram positive</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Penicillinase negative (28)</td>
<td>0.12 0.03</td>
<td></td>
</tr>
<tr>
<td>Penicillinase positive (27)</td>
<td>0.12 0.03</td>
<td></td>
</tr>
<tr>
<td>Meticillin resistant (10)</td>
<td>8 4</td>
<td></td>
</tr>
<tr>
<td><em>Streptococcus pneumoniae</em></td>
<td>0.015 &lt;0.015</td>
<td></td>
</tr>
<tr>
<td>Penicillin susceptible (20)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Penicillin resistant*** (10)</td>
<td>0.25 0.12</td>
<td></td>
</tr>
<tr>
<td>β-hemolytic streptococci</td>
<td></td>
<td></td>
</tr>
<tr>
<td>groups C, G (20)</td>
<td>0.008 &lt;0.015</td>
<td></td>
</tr>
<tr>
<td><em>Streptococcusagalactiae</em> (30)</td>
<td>0.06 0.03</td>
<td></td>
</tr>
<tr>
<td><em>Enterococcus faecalis</em> (28)</td>
<td>4 1</td>
<td></td>
</tr>
<tr>
<td><strong>Anaerobes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Peptostreptococcus species</em> (11)</td>
<td>0.25 ND</td>
<td></td>
</tr>
<tr>
<td><em>Bacteroides fragilis</em> (31)</td>
<td>0.25 ND</td>
<td></td>
</tr>
<tr>
<td><em>Clostridium species</em> (12)</td>
<td>0.12 ND</td>
<td></td>
</tr>
</tbody>
</table>

NOTE. This table was adapted with permission from [12]. ND = not done.

* Includes *K. oxytoca* (seven strains) and *K. pneumoniae* (25 strains).
** Of the tested isolates, 2% were resistant as defined by established NCCLS (National Committee for Clinical Laboratory Standards) criteria and by an MIC of >8 mg/L for meropenem. The finding that meropenem and imipenem have equivalent activity is not consistent with other studies, which have found meropenem to be more active against *P. aeruginosa*.
*** Penicillin MICs of ≥0.12 mg/L or a zone diameter of ≥19 mm for 1-µg of methicillin.

15%–25% is recovered as the open β-lactam ring metabolite [5, 18, 23, 24] (data on file, Zeneca Pharmaceuticals). The recovery of meropenem in urine is similar to that of imipenem coadministered with cilastatin, thus demonstrating the stability of meropenem to DHP-I degradation [19].

Some renal metabolism of meropenem may occur, especially in individuals who metabolize imipenem at high rates when it is given alone. Recovery of meropenem, which ranged from 62.2% to 78.2%, was correlated with recovery of imipenem in the same healthy subjects (range, 15.2%–33.2%). Even individuals who metabolize meropenem to a greater degree may still safely receive this drug without an inhibitor of DHP-I [24].

Probenecid interaction studies have established that meropenem is cleared by both glomerular filtration and tubular secretion. In the presence of probenecid, which blocks secretion at the proximal convoluted tubule, AUC values for meropenem after administration of 500 mg iv over 30 minutes (●), 500 mg iv over 5 minutes (□), and 500 mg im (○) to healthy volunteers (data on file, Zeneca Pharmaceuticals).

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Figure 2. Mean plasma concentration-time profiles for meropenem after administration of 500 mg iv over 30 minutes (●), 500 mg iv over 5 minutes (□), and 500 mg im (○) to healthy volunteers (data on file, Zeneca Pharmaceuticals).

Figure 3. Mean plasma concentration-time profiles for meropenem (○) and its microbiologically inactive metabolite ICI 213,689 (●) in eight young (----) and eight elderly (-----) healthy men following a 30-minute infusion of 0.5 g of meropenem. Adapted with permission from Ljungberg and Nilsson-Ehle [23].
maximal concentration of drug (C<sub>max</sub>) over this fourfold span [18]. In another study, the maximum therapeutic dose of meropenem was increased to 2 g, and the AUC increased 11-fold from 250 mg to 2 g. As shown in figure 5, the dose-response graph relating the AUC for meropenem to the dose is approximately linear from 250 mg to 2 g (data on file, Zeneca Pharmaceuticals), indicating essential dose proportionality.

**Renally impaired patients.** Both renal impairment and age-related declines in the glomerular filtration rate influence the pharmacokinetics of meropenem and its metabolite (figures 4 and 6), warranting commensurate dosage reductions [5, 22, 23, 25, 26]. Leroy and co-workers [5] studied six healthy volunteers and 16 patients with moderate to severe renal impairment who received a 30-minute infusion of meropenem (500 mg). The terminal t<sub>1/2</sub> of unchanged meropenem increased in relation to the degree of renal impairment, as did the AUC value. The t<sub>1/2</sub> was 1.2 hours for healthy volunteers, compared with >10 hours for patients with end-stage renal disease, while the AUC rose from 28 to 416 μg·h/mL across the same groups. After treatment with meropenem, the C<sub>max</sub> also rose significantly for patients with renal impairment compared with healthy volunteers (42.5 vs. 21.1 μg/mL; P = .1).

Evaluating a similar group of 23 healthy volunteers and patients with renal impairment, Christensson and colleagues [22] observed a rise in the meropenem t<sub>1/2</sub> from 0.9 hour in healthy volunteers to 6.8 hours in patients with end-stage renal disease. The t<sub>1/2</sub> of the open β-lactam ring metabolite (ICI 213,689) was 2.31 hours in healthy volunteers and 23.6 hours in patients with a glomerular filtration rate of 5–29 mL/min; the t<sub>1/2</sub> could not be calculated for patients with end-stage renal disease because the concentrations of meropenem remained stable during the 48-hour post-dose interval.

Dosing alterations in patients with renal impairment should be based on their renal status as outlined in table 3 [22]. The

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**Table 2.** Pharmacokinetics of meropenem in healthy volunteers.

<table>
<thead>
<tr>
<th>Investigator [reference] (no. of volunteers)</th>
<th>Dose (mg)</th>
<th>Route of administration</th>
<th>C&lt;sub&gt;max&lt;/sub&gt; (μg/mL)</th>
<th>AUC (μg·h/mL)</th>
<th>V&lt;sub&gt;a&lt;/sub&gt; (L)</th>
<th>t&lt;sub&gt;1/2&lt;/sub&gt; (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leroy et al. [5] (6)</td>
<td>500</td>
<td>IV bolus</td>
<td>21.1</td>
<td>28.0</td>
<td>0.39*</td>
<td>1.24</td>
</tr>
<tr>
<td>Christensson et al. [22] (6)</td>
<td>500</td>
<td>30-min iv infusion</td>
<td>30.3</td>
<td>36.0</td>
<td>0.21*</td>
<td>0.93</td>
</tr>
<tr>
<td>Ljungberg and Nilsson-Ehle [23] (8)</td>
<td>500</td>
<td>30-min iv infusion</td>
<td>35.6</td>
<td>39.6</td>
<td>11.7</td>
<td>0.81</td>
</tr>
<tr>
<td>Burman et al. [24] (6)</td>
<td>500</td>
<td>30-min iv infusion</td>
<td>24.8</td>
<td>27.2</td>
<td>20.4</td>
<td>0.83</td>
</tr>
<tr>
<td>Bax et al. [18] (6)</td>
<td>500</td>
<td>30-min iv infusion</td>
<td>25.6</td>
<td>30.1</td>
<td>19.1</td>
<td>0.97</td>
</tr>
<tr>
<td>Bax et al. [18] (6)</td>
<td>1,000</td>
<td>30-min iv infusion</td>
<td>55.4</td>
<td>66.9</td>
<td>17.8</td>
<td>0.96</td>
</tr>
<tr>
<td>Nilsson-Ehle et al. [19] (8)</td>
<td>1,000</td>
<td>30-min iv infusion</td>
<td>61.6</td>
<td>77.5</td>
<td>12.5</td>
<td>0.98</td>
</tr>
<tr>
<td>Wise et al. [21] (6)</td>
<td>1,000</td>
<td>IV bolus</td>
<td>28.3</td>
<td>66.9</td>
<td>20.6</td>
<td>1.10</td>
</tr>
</tbody>
</table>

**NOTE.** AUC = area under the curve; C<sub>max</sub> = maximal concentration of drug; t<sub>1/2</sub> = half-life; V<sub>a</sub> = apparent volume of distribution of steady state.
dose should not be reduced in patients whose glomerular filtration rate is >50 mL/min. This dosage schedule for patients with normal renal function is based on the usual recommended “unit” dose of 500 mg to 1 g by iv administration every 8 hours depending on the type and severity of the infection, the susceptibility of the pathogen, and the condition of the patient. The recommended doses for patients with febrile neutropenia or meningitis are 1 g every 8 hours and 2 g every 8 hours, respectively.

Meropenem and its open β-lactam ring metabolite (ICI 213,689) are cleared readily by hemodialysis; therefore, meropenem must be administered after this process [25]. No data on the effect of peritoneal dialysis on the pharmacokinetics of meropenem have been published.

Elderly patients. Ljungberg and Nilsson-Ehle [23] determined that both total and renal clearance of meropenem are significantly correlated with glomerular filtration rate. As a result of age-related declines in the glomerular filtration rate, the mean terminal t_{1/2} of meropenem in healthy elderly volunteers (mean age, 73 years) was prolonged significantly compared with that in eight younger volunteers (mean age, 28 years), with half-lives of 1.27 and 0.81 hours, respectively (P <.001). Similarly, the t_{1/2} of the microbiologically inactive metabolite ICI 213,689 increased by ~50% in persons over 65 years of age compared with their younger counterparts (3.12 vs. 1.98 hours, respectively). Nonrenal clearance of meropenem also decreases in the elderly group, presumably as a result of slower metabolic transformation of the meropenem molecule. Consequently, dose adjustment should be considered for elderly patients when there is evidence of significant renal impairment (e.g., creatinine clearance of <50 mL/min) [23].

Infants and children. Several investigators have measured the pharmacokinetics of meropenem in infants and children [17, 27–36]. Overall, these studies have found that doses ranging from 10–40 mg/kg produce pharmacokinetic data similar to those for adults receiving doses of 500 mg, 1 g, or 2 g (table 4). As with adults, C_{max} and AUC values tend to increase linearly with dose, rising three- to fourfold over the dose range of 10–40 mg/kg (data on file, Zeneca Pharmaceuticals).

Blumer and co-workers [38] evaluated the pharmacokinetics of meropenem in 63 children who ranged in age from 2 months to 12 years and concluded that a meropenem dose of 20 mg/kg administered every 8 hours will maintain meropenem concentrations above the MIC for essentially all susceptible bacterial pathogens. The mean (±SD) elimination t_{1/2} was 1.13 ± 0.15 hours, the V_{D} was 0.43 ± 0.06 L/kg, the total clearance was 5.63 ± 0.75 mL/(min·kg), and the renal clearance was 2.53 ± 0.50 mL/(min·kg).

Approximately 55% of the administered dose was recovered as parent compound in the urine during the 12 hours after dosing, confirming the relative stability of meropenem to DHP-I degradation in children. The t_{1/2} of meropenem tends to be somewhat longer in younger children; the mean t_{1/2} is

<table>
<thead>
<tr>
<th>Creatinine clearance (mL/min)</th>
<th>Meropenem dose (mg)*</th>
<th>Frequency of administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>26–50</td>
<td>500–2,000</td>
<td>Every 12 h</td>
</tr>
<tr>
<td>10–25</td>
<td>250–1,000</td>
<td>Every 12 h</td>
</tr>
<tr>
<td>&lt;0</td>
<td>250–1,000</td>
<td>Every 24 h</td>
</tr>
</tbody>
</table>

* Based on usual “unit” dose of 500 mg to 2 g by iv administration every 8 hours depending on the type and severity of the infection, the known or expected susceptibility of the pathogen(s), and the condition of the patient.
Penetration of meropenem was rapidly achieved in blister fluid,” Trager et al. [43] found that in blister fluid induced by cantharidin, meropenem concentrations were 87.1% of those in serum. Wise et al. [21] found that cantharidine-induced inflammatory fluid penetration of meropenem was rapid in six healthy volunteers given a single 1-g iv dose. In this study, the penetration of meropenem in blister fluid was 111% that of plasma concentration.

**Abdominal tissues.** Penetration of meropenem into peritoneal fluid, bile, the colon, the gallbladder, omentum, the stomach, fascia, muscles, and skin after a single 1-g iv dose infused over 30 minutes was studied in 66 patients undergoing elective intraabdominal surgery by Condon and colleagues [44]. Meropenem rapidly penetrated abdominal tissues, attaining levels above the MIC<sub>90</sub> for most intraabdominal pathogens. The following peak meropenem concentrations were achieved in most tissues within 1 hour: plasma, 27.3 μg/mL; peritoneal fluid, 12.2 μg/mL; colon, 2.6 μg/g; and gallbladder, 3.2 μg/g.

**Bile.** Although biliary excretion of meropenem is generally low, Granai and colleagues [45] found that bile concentrations in 24 patients undergoing endoscopic retrograde cholangiography exceeded the MIC<sub>90</sub> values for pathogens most frequently associated with biliary tract infections. After a single 1-g dose of meropenem infused over 15–20 minutes, the bile concentrations ranged from 0.7 to 25.7 mg/L (mean, 11.1 mg/L). Corresponding plasma meropenem concentrations at the time of endoscopic retrograde cholangiography ranged from 2.6 to 44.3 mg/L (mean, 17.5 mg/L). The bile:plasma ratio varied from 0.3 to 3.2 (mean, 1.0).

Despite being generally lower in patients with biliary-tree obstruction, bile concentrations of meropenem in 13 such patients nevertheless exceeded the MIC<sub>90</sub> values for the most common biliary pathogens even at the lowest meropenem concentration recorded (0.7 mg/L).

Furukawa et al. [46] and Shimizu et al. [47] reported similar concentrations of meropenem in the biliary tracts of patients undergoing cholecystectomy. After a 30-minute infusion of a 0.5-g dose of meropenem, meropenem concentrations in bile were 0.2–16.1 μg/mL for 7 of 10 patients and were 0.4–7.6 μg/g in gallbladder tissue for 6 of 10 patients [45]. Similarly, Shimizu and colleagues [47] administered meropenem (500 mg iv) to five patients before they underwent cholecystectomy. Peak meropenem concentrations in bile were 0.14–9.78 μg/mL. Peak meropenem levels in bile ranging from 2.2 to 12.0 μg/mL were observed in other studies [48, 49].

In another tissue penetration study, peak meropenem concentrations in bile and muscle were achieved within 2–5 hours after the dose was administered. Concentrations in bile increased with time, from 4.9 μg/mL at 0.5–1.5 hours to 8.4 μg/mL at 1.5–3.0 hours, and to 17.7 μg/mL at 3–5 hours, indicating active excretion of the drug into bile [44].

**Gynecologic tissues.** Gall and co-workers [50] studied the penetration of meropenem into the tissues of 64 patients undergoing elective gynecologic surgery. In all tissues evaluated,
the following peak meropenem concentrations were achieved within 1.5 hours of a single preoperative 500-mg iv dose: peritoneal fluid, 8.8 μg/mL; cervix, 7.0 μg/g; endometrium, 2.3 μg/g; fallopian tube, 1.9 μg/g; myometrium, 3.6 μg/g; ovary, 2.3 μg/g; and uterus, 2.3 μg/g.

CSF. Although meropenem penetrates the intact blood-brain barrier poorly, sufficiently high CSF concentrations of the drug are achieved in order to eradicate most pathogens in patients with meningitis. In 19 children ranging in age from 1 month to 15 years (68% <2 years old), a meropenem dose of 40 mg/kg produced adequate CSF concentrations of 0.9–2.8 mg/L [51].

Meropenem administered at a dosage of 40 mg/kg three times daily, together with tobramycin for 18 weeks, proved...
safe and effective in one case of iatrogenic meningitis (a 24-year-old man with lymphoblastic lymphoma) caused by two distinct strains of *Pseudomonas aeruginosa* that was resistant to cefazidime, amikacin, and ciprofloxacin [52]. A second course of meropenem was needed for the management of recurrence of disease, but the infection again resolved rapidly. After a 2-g dose of meropenem (38.5 mg/kg) was administered, CSF concentrations ranged from 0.5 to 1.6 mg/L [52].

Respiratory tract. Extensive tissue penetration, as expressed by high tissue-to-plasma concentration ratios, was observed by Thys [53] in a study of nine patients who were undergoing surgery for bronchial malignancies. In patients who were treated preoperatively with a single dose of meropenem (1 g iv), peak concentrations of meropenem were reached at 2 hours in the lung and pleura (4.83 μg/g and 3.62 μg/g, respectively), whereas peak concentrations in bronchial mucosa and bronchial secretions were reached in 1 hour (4.53 μg/g and 6.17 μg/mL, respectively).

Tissue penetrations (expressed as percentage of tissue vs. plasma concentration) of 40% in the lung, 38% in the bronchial mucosa, 24% in the pleura, and 52% in bronchial secretions were reported in this study. Comparable data for the concentrations of meropenem in bronchial secretions have also been reported in several small studies [54, 55].

Urinary tract. As shown in figure 7E, urine concentrations of meropenem exceed 1 μg/mL for at least 12 hours, even with doses as low as 250 mg. Eight patients who received a 30-minute infusion of meropenem (500 mg) after undergoing transurethral resection exhibited a 16% penetration of prostate tissue as a fraction of plasma level [56].

Other tissues and fluids. Newsom and co-workers [57] studied 32 patients who were treated prophylactically with meropenem (10-minute iv infusion of 1 g) before undergoing cardiac-valve surgery. Atrial tissue samples obtained 0.27–3 hours after dosing showed mean tissue levels of 7.5 μg/g (range, 0.6–15.8 μg/g). The tissue-to-plasma concentration ratios ranged from 22% to 42% at hours 0 to 1 and 2 to 3, respectively.

The peak concentrations of meropenem in the aqueous humor ranged from 0.17 to 0.93 mg/L, and the peak tear-fluid concentration was 1.25 mg/L after a 500-mg iv dose administered to nine healthy volunteers. Bacteriologic eradication was complete in 20 patients with eye disorders who were treated with meropenem (250–500 mg iv q.d., b.i.d., or t.i.d.). The overall clinical efficacy in these patients reached 90% [58].

Preclinical Safety Data

As noted previously, preclinical studies on meropenem’s effects in the CNS indicated that meropenem had less epileptogenic potential than did imipenem. Preclinical studies have also demonstrated a favorable safety profile in terms of meropenem’s effects in the renal and digestive systems.

The safety of meropenem with regard to nephrotoxicity has been assessed by Topham and co-workers [59]. Whereas administration of cefaloridine (850 mg/kg) and imipenem (150 mg/kg) to rabbits resulted in histopathologic changes consistent with renal tubular necrosis, minimal changes to the kidneys were evident after administration of cefotaxime, cefazidime, or meropenem (each at 400 mg/kg); similar patterns were evident in cynomolgus monkeys. On the basis of these findings, meropenem was judged to have a low potential for nephrotoxicity.

Unlike many other broad-spectrum antimicrobial agents, meropenem exerts only mild or minimal effects on the intestinal microflora, and these effects subside within 2 weeks after termination of therapy [60]. In 10 healthy volunteers treated with 500 mg of iv meropenem, colony counts of enterobacteria, streptococci, clostridia, *Bacteroides* species, and gram-negative cocci diminished, whereas those of enterococci rose. The number of gram-positive cocci and rods was unaltered. This relative lack of adverse changes in intestinal aerobes and anaerobes was consistent with the finding of no measurable fecal excretion of meropenem [60].

Summary

Meropenem, a new β-lactam antibiotic of the carbapenem family, differs from imipenem in several structural features. These structural differences explain the relative stability of meropenem to DHP-I hydrolysis [1, 7, 8]. Structural differences may explain why meropenem has a lower observed potential for induction of epileptogenic activity than does imipenem [2, 3].

In clinical trials, seizures have been reported in up to 3% of patients receiving imipenem [1, 61]. The incidence of seizures is considerably higher (20%–32%) in patients with renal impairment or underlying CNS disease as well as in patients who receive doses of imipenem that are larger than those recommended by the manufacturer (e.g., >50 mg/kg or >4 g/d). The fact that the epileptogenic activity of meropenem is reduced compared with that of imipenem could markedly increase the therapeutic effects of carbapenem treatment of bacterial infections while reducing the toxicity of this drug.

Meropenem has a profile of bacteriologic activity similar to that of imipenem [13] but has significantly higher in vitro activity against gram-negative aerobes, lesser activity against staphylococci, and equivalent activity against streptococci and anaerobes [11, 13–15].

The pharmacokinetics of meropenem are similar to those of other parenterally administered β-lactam antibiotics, including imipenem, that have low protein binding and predominantly renal excretion. Meropenem is metabolized to a single, microbiologically inactive metabolite and is cleared largely through renal excretion, with 75%–95% of an iv dose being recovered in urine as either meropenem or its metabolite.

Dose proportionality is shown with meropenem doses between 250 mg and 2 g [17]. Adequate serum levels above the MICs for most susceptible pathogens may be obtained with a
dosing schedule of once every 8 hours for most infections. Studies in animal infection models have demonstrated that the duration of time that serum levels exceed the MIC is the important determinant of in vivo efficacy for meropenem [62].

The pharmacokinetics of meropenem in infants and children is similar to that in adults [27–37]. Dose proportionality is observed over the dose range of 10–40 mg/kg [38].

Tissue penetration of meropenem has been examined in a wide range of infections and tissues. Meropenem levels equaled or exceeded the MICs needed to treat the most important pathogens in abdominal tissues [44], bile [45–49], blister fluid or inflammatory exudate [21, 43], CSF [51], gynecologic tissues [50], respiratory tract tissues [53], and urinary tract tissues (data on file, Zeneca Pharmaceuticals).

Meropenem appears to have a favorable safety profile. Preclinical studies suggest that meropenem has a low potential for nephrotoxicity [59], although adjustments must be made in the dose for patients with renal impairment [5] as well as for elderly patients with a creatinine clearance of ≤50 mL/min [23]. No adjustments need to be made for patients with hepatic impairment [40]. Meropenem has only mild, transient effects on gastrointestinal microflora [60].

References


