Carbapenem and Monobactam Antibiotics

Imipenem-Cilastatin & Meropenem

I. STRUCTURE AND MECHANISM OF ACTION

Imipenem (N-formimidoyl thienamycin) is a more stable amide derivative of thienamycin. Thienamycin was isolated from the Spanish soil organism *Streptomycetes cattleya* in the early 1970s. Imipenem is the first of a new class of carbapenem antibiotics. A carbapenem is characterized by replacement of the sulfur atom at the 1 position of the 5-membered B-ring by carbon atom and the inclusion of a double bond in the B-ring. In contrast to the conventional cis-configuration of the acyl side chain in penicillins, the hydroxyethyl side chain of imipenem is in a trans configuration which results in unusual stability to β-lactamases. Imipenem is rapidly inactivated by renal brush border dehydropeptidase-1, resulting in low urine concentrations when administered alone. Consequently, Merck developed cilastatin, a potent inhibitor of dehydropeptidase-1. Co-administration of cilastatin increases the amount of imipenem excreted unchanged in urine to ~70%. Meropenem is a new carbapenem that has a similar spectrum to that of imipenem. Unlike imipenem, meropenem is not hydrolyzed renal dehydropeptidase and therefore can be administered alone (without cilastatin).

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\text{Imipenem}
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Imipenem's and meropenem's mechanism of action is similar to other β-lactam antibiotics. In gram-negative bacteria, imipenem has high affinity for PBPs 2, 1a and 1b. Binding to these PBPs leads to spheroplast formation and rapid cell lysis. Both meropenem and imipenem are highly resistant to β-lactamases, however, they are potent inducers of β-lactamase synthesis, and thus should not be used prior to or with other β-lactam antibiotics. Imipenem is slightly more active against gram positive bacteria, whereas meropenem is slightly more active against gram negative bacteria.

II. SPECTRUM

A. Gram Positive Bacteria

1. Similar to first generation cephalosporins
   a. *Streptococcus sp.* (except for penicillin-resistant *Strep. pneumoniae*)
   b. *Staphylococcus sp.* (except for methicillin-resistant Staph.)
   c. *Listeria monocytogenes* (meropenem much more active)
   d. *Enterococcus faecalis* (bacteriostatic only - combine with AGs)
B. Gram Negative Bacteria

1. Enterobacteriaceae
   
a. *Acinetobacter sp.*, *Citrobacter sp.*, *Enterobacter cloacae*, *E. coli*, *Klebsiella sp., Proteus mirabilis, Providencia sp., Salmonella sp., Shigella sp., Yersinia*

2. *Pseudomonas aeruginosa* (MIC$_{90}$ generally less than 4 µg/ml). Imipenem is synergistic with aminoglycosides.

3. *Haemophilus sp.* (includes strains resistant to ampicillin, chloramphenicol, and TMP-SMX), *Neisseria sp.*, and *Moraxella catarrhalis*

C. Anaerobes

1. Gram positive anaerobes - *Actinomyces sp., Clostridia sp., Eubacterium, Peptococcus, Peptostreptococcus, Propionobacterium*

2. Gram positive anaerobes - all *Bacteroides sp.* and *Fusobacterium sp.*

D. Bacteria that are resistant

1. *Enterococcus faecium*

2. *Stenotrophomonas (Xanthomonas) maltophilia* and *Pseudomonas cepacia*

3. Some resistance observed in indole + *Proteus, Morganella, & Providencia* (MIC$_{90}$ in the 2-5 µg/ml range) and *Pseudomonas*

4. Methicillin-resistant *Staph.*

5. *Clostridium difficile* (MIC = 2-16 µg/ml)

6. Intracellular organisms - *Chlamydia, Mycoplasma, Mycobacterium sp.*

III. USES

A. Empiric therapy for bacteremia (in combination with aminoglycosides) - at least as effective as 3rd generation cephalosporins.

B. Nosocomial-acquired lower respiratory tract infections

C. Serious intra-abdominal infections (good anaerobic activity). For pelvic inflammatory disease - combine with macrolide or tetracycline to cover *Chlamydia trachomatis.*

D. *Pseudomonas aeruginosa* infections (in combination with aminoglycosides).
E. Osteomyelitis due to gram negative organism or mixed aerobic-anaerobic infections.

F. Meningitis - Meropenem had similar cure rates compared to cefotaxime in children. A small study in adults (23 patients) found a 100% cure rate compared to 77% with cefotaxime or ceftriaxone. Meropenem would be preferred over Primaxin for meningitis.

G. DO NOT USE for surgical prophylaxis, community-acquired infections, or ALONE for Ps. aeruginosa or enterococcal infections.
IV. DISPOSITION AND PHARMACOKINETICS

A. Given as fixed combination of imipenem:cilastatin (1:1) parenterally

B. Peak serum levels - 50-55 µg/ml after 1g dose of imipenem

C. Half-life of approximately 1 hr. in normals. Increases to 4 hr in patients with creatinine clearance of <10 ml/min (16 h for cilastatin component). Renal excretion - 70%. Likewise, for meropenem, approximately 70% of the dose is excreted unchanged in the urine.

D. Imipenem levels in the CSF in meningitis patients were 0.5-11 µg/ml

V. ADVERSE EFFECTS

A. Generally well tolerated - some cross-sensitivity with penicillin allergy

B. GI problems are most common (1-2%). Pseudomembranous colitis (0.1%).

C. Seizures - observed in 0.3-1.0% of patients treated with imipenem, usually in the elderly and in patients with underlying abnormality of the CNS (Epilepsy, head injury, history of CVA, alcoholism). Seizures appear to be increased when administered with ganciclovir (probably due to ganciclovir-induced renal dysfunction). Meropenem is unlikely to cause seizures.

D. Enterococcal superinfection - much less frequent than with 3rd gen. cephalosporins.

VI. PRODUCTS AND DOSING

**Imipenem**

Powder for IV Injection: 250 mg imipenem/250 mg cilastatin and 500 mg imipenem/500 mg cilastatin in vials, infusion bottles, and ADD-Vantage vials (Primaxin I.V.® – MSD).

Powder for IM Injection: 500 mg imipenem/500 mg cilastatin and 750 mg imipenem/750 mg cilastatin in vials (Primaxin I.M.® - MSD).

Stable for 4 hours at room temp. and 24 h refrigerated (stability doubled if reconstituted in 0.9% NaCl)

Moderate severity infections: 500 mg q 6 or 8 h
Severe and life-threatening infections: 500 mg q 6 h. Do not exceed 4 g/d
Pseudomonal infections: 1g q 6 or 8 h.
Complicated UTIs: 500 mg q 6 h

Intraabdominal infections: 750 mg q 12 h intramuscularly.

**Meropenem**
Powder for IV injection: 500mg and 1g (Merrem® Astra-Zeneca) in vials and ADD-Vantage vials.
Adults: 1 gram IV every eight hours
Children: 20 mg/kg (maximum 1 g) every eight hours for intra-abdominal infections, and 40 mg/kg (maximum 2 g) every 8 h for meningitis.
Aztreonam

I. STRUCTURE AND MECHANISM OF ACTION

Aztreonam is a synthetic monobactam antibiotic. The β-lactam ring is activated by sulfonic acid group on the nitrogen. Aztreonam binds specifically to PBP3 of gram negative and inhibits cell wall synthesis. This inhibition results in the formation of elongated and filamentous forms which eventually lyse. It is highly resistant to β-lactamases and unlike imipenem is not an inducer of these enzymes. It binds poorly to PBPs of gram positive bacteria and anaerobes and thus has only a limited gram positive spectrum.

II. SPECTRUM

A. Enterobacteriaceae - highly active against most aerobic, gram negative bacteria
1. *E. coli, Klebsiella sp., Serratia marcescens, Proteus sp., Salmonella* (MIC ≤ 2 µg/ml)
2. *Enterobacter sp., Citrobacter sp.* (MIC = 1-8 µg/ml)

B. *H. influenzae, Neisseria sp., and Moraxella catarrhalis*

C. *Pseudomonas aeruginosa* (90% have MIC < 12.5 µg/ml) - covers most gentamicin & carbenicillin-resistant strains.

D. Gram negative bacteria that are resistant
1. *Acinetobacter, Achromobacter, and Alcaligenes sp.*
2. *Pseudomonas cepacia & Xanthomonas maltophilia*

III. USES

A. Gram negative septicemia

B. Empiric treatment of febrile episodes in neutropenic patients (in combination with vancomycin)

C. Complicated and uncomplicated UTIs due to gram negative bacteria - useful alternative to aminoglycosides or cephalosporins

D. Gram negative osteomyelitis or septic arthritis
IV. DISPOSITION AND PHARMACOKINETICS

A. Peak serum levels after 1g 30 min IV infusion are 90-160 µg/ml. With q 8 h dosing, trough levels are 1.5 µg/ml.

B. Widely distributed. CSF concs. = 7.2 µg/ml in adults 2-8 hrs after 2 g IV dose. 30-50% protein bound.

C. Excreted renally (58-74% unchanged). Normal half-life is 1.3-2.2 hrs. Reduce dose by 75% in anephric patients. Half-life in neonates <7 days is 5-10 hrs.

V. ADVERSE EFFECTS

A. Very well tolerated. Some skin rashes (1%).

B. Transient Increase in liver enzymes (2-4%)

C. Very low cross-sensitivity with penicillins & cephalosporins

D. Major problem is superinfection due to enterococci (~10-20%)

VI. PRODUCTS AND DOSING

Powder for Injection: 500 mg, 1 g, and 2 g in 15 ml vials and 100 ml infusion bottles (Azactam® - Bristol-Myers Squibb).

Incompatible with nafcillin sodium, cephradine, and metronidazole.

Moderately severe systemic infections: 1 or 2 g q 8 -12 hrs  
Severe or life-threatening infections: 2 g q 6-8 hrs  
Urinary tract infections: 500 mg - 1 g q 8-12 hrs.