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## Revue comparative de l'imipénème/cilastatine versus méropénème

### Comparative review of imipenem/cilastatin versus meropenem

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#### Contribution of authors

C.M., M.B., M.B., S.M., P.C., and L.P. critically reviewed the article.

#### Disclosure of interest

The authors declare no conflict of interest.

**Keywords:** carbapenem, imipenem/cilastatin, meropenem, antibiotic stewardship

**Mots clés :** carbapénème, imipénème/cilastatine, méropénème, bon usage des antibiotiques

## Résumé

**Introduction.** Les carbapénèmes sont des molécules antibactériennes à large spectre. En France, l'imipénème-cilastatine et le méropénème sont les deux principales molécules utilisées dans les services de soins.

**Objectif.** L'objectif était d'évaluer les forces et les faiblesses de ces deux molécules en considérant leurs propriétés pharmacocinétiques, pharmacodynamiques, microbiologiques et cliniques. Nous avons démontré que l'imipénème-cilastatine et le méropénème ne sont pas semblables.

**Méthode.** Revue de la littérature en interrogeant le réseau MEDLINE.

**Résultats.** L'imipénème-cilastatine est la première des molécules commercialisées de la classe des carbapénèmes. Elle est plus efficace contre les cocci à Gram-positif. Sa stabilité ne permet pas de perfusions longues et son principal effet secondaire sur le système nerveux central en limite son utilisation. Le méropénème est plus efficace contre les bacilles à Gram-négatif. Sa stabilité et ses moindres effets secondaires l'opposent à l'imipénème-cilastatine.

**Conclusion.** L'analyse de la littérature actuelle nous fait préférer le méropénème dans son utilisation quotidienne dans les services de soins lorsqu'un carbapénème doit être utilisé.

## **Abstract**

**Introduction.** Carbapenems are broad-spectrum antibacterial molecules. Imipenem-cilastatin and meropenem are the two main molecules used in French healthcare services.

**Objective.** We aimed to evaluate the relative strengths and weaknesses of these two molecules by considering their pharmacokinetic, pharmacodynamic, microbiological, and clinical properties. We demonstrated that imipenem-cilastatin and meropenem are not alike.

**Method.** Review of the literature by querying the MEDLINE network.

**Results.** Imipenem-cilastatin is the first marketed molecule of the carbapenem class. It is more effective against Gram-positive cocci. Its stability does not allow for long infusions and its main adverse effect on the central nervous system limits its use. Meropenem is more effective against Gram-negative bacilli. Its stability and its milder adverse effects distinguish it from imipenem-cilastatin.

**Conclusion.** Meropenem is preferred for daily use in healthcare services when carbapenems are to be used.

## Introduction

Thienamycin is an antibiotic produced by *Streptomyces cattleya*, a Gram-positive filamentous bacterium belonging to the Actinomycetes order. Thienamycin was discovered in 1976 and led to medical advances. However, this natural antibiotic is unstable and a semi-synthetic derivative (N-formimidoyl) of thienamycin was developed as early as 1980, *i.e.* imipenem. Imipenem needs to be combined with cilastatin, a dehydropeptidase-1 inhibitor (DHP-1) which is an enzyme produced by the proximal tubules. The role of this inhibitor is two-fold: to slow down the rapid *in vivo* deterioration of the antibiotic and to prevent natural nephrotoxicity of imipenem.

Imipenem thus became the first carbapenem antibiotic in 1990, soon followed by ertapenem (2002), meropenem (2008), and doripenem (2009).

Ertapenem has different pharmacokinetic properties and modalities of use than other carbapenems, especially its long half-life (4 hours) enabling a single daily injection and patient discharge from hospital. However, ertapenem is not active against enterococci, *Acinetobacter baumannii*, and *Pseudomonas aeruginosa*. It is therefore not the reference molecule, especially for the empirical treatment of nosocomial infections.

Doripenem stopped to be commercialized in 2014. The two remaining carbapenems, *i.e.* imipenem/cilastatin and meropenem, are closely related and often used indistinctly in hospital settings despite specific differences.

We aimed to make an inventory of the differences between imipenem-cilastatin and meropenem with a potentially significant clinical impact, to guide prescribers when penem prescription is required.

## **Material and methods**

We consulted the PubMed database to perform the present literature review.

We included randomized and non-randomized human studies performed in controlled and uncontrolled groups, and published in English from June 1980 to August 2018. We included meta-analyses, literature reviews, and phase 1 and 2 clinical trials. We also included articles from the references of these selected articles. The following MeSH terms were used: “carbapenem”, “imipenem”, “meropenem”, “administration”, “dosage”, “adverse effect”, “metabolism”, “pharmacokinetics”, “pharmacology”, “therapeutic use”, “toxicity”, “brain”, “microbiota”, “obesity”, “critically ill”, “children”, and “pregnancy”. Articles were selected based on their clinical relevance, quality, and reliability of studies.

## **RESULTS**

### **1- Chemical structure**

Carbapenems belong to the beta-lactam family.

An atom of carbon instead of an atom of sulfur in position 1 and an unsaturated binding in C2-C3 position distinguish them from penicillins (Figure 1).

Compared with imipenem, meropenem is not degraded by DHP-1, hence the absence of binding to a DHP-1 inhibitor. Moreover, modifications of the substitute in C2 position are responsible for the increased activity of meropenem against Gram-negative bacilli [1-3].

### **2- Mechanism of action**

Similarly to all penicillins, carbapenems act on penicillin-binding proteins (PBP). The bactericidal action occurs through bacterial lysis by inhibiting the transpeptidation step of

peptidoglycan with higher affinity for PBPs than other beta-lactams [1]. Inhibition of PBP2 induces the formation of spheroplast without filamentation, but with rapid bactericidal action; while PBP3 inhibition produces filamentation and small release of endotoxin for Gram-negative bacteria [4-6].

Affinity for PBP varies by bacteria. For *Escherichia coli* and compared with meropenem, imipenem has a four-fold binding activity with PBP1a and PBP1b and a 10-fold binding activity with PBP5, while meropenem has a higher binding affinity with PBP3 and PBP6 [4]. On the contrary, for *Pseudomonas aeruginosa* the binding affinity of meropenem is higher with PBP2 and PBP3 than that of imipenem [4].

### **3- Mechanism of resistance**

Similarly to beta-lactams, there are four types of mechanism of resistance to carbapenems: i) production of zinc-dependent metallo- $\beta$ -lactamases, ii) decreased permeability of the external membrane of Gram-negative bacilli, iii) presence of efflux pumps, and iv) modification of molecular target (PBP).

Mechanisms of resistance differ by bacteria. Resistance of Gram-positive cocci is related to the poor affinity for some PBPs: PBP5 for *Enterococcus faecium*, PBP2a for methicillin-resistant *Staphylococcus aureus*. Minimum inhibitory concentrations (MICs) vary by bacteria and by molecules. *Enterococcus faecalis* remains only susceptible to imipenem with a bacteriostatic effect [1]. The same goes for pneumococci resistant to penicillins through PBP1a and PBP1b modification. Resistance of Gram-negative bacilli is most often an enzyme resistance due to the production of carbapenemases grouped into three classes: A, B, and D

[7], and to the reduced permeability of the external membrane [8]. There is no difference on that matter between imipenem and meropenem.

#### **4- In vitro activity** (Tables 1, 2, 3)

The antibacterial spectra of imipenem and meropenem can be distinguished by their different intrinsic activity [2, 9-18]. Gram-positive cocci have higher susceptibility to imipenem while Gram-negative bacilli have higher susceptibility to meropenem, with a 16-fold difference in MICs [8].

#### **5- Pharmacodynamics/pharmacokinetics** [1-3, 19-25]

These two molecules have comparable pharmacokinetic properties. Only protein binding is weaker for meropenem (Table 4).

Penems are mainly eliminated by the renal route, and elimination is approximately 30% (Table 4).

In patients presenting with renal failure, the elimination half-life of carbapenems increases and is close to five hours for imipenem/cilastatin and seven hours for meropenem [26]. Plasma concentrations may be insufficient at dosages recommended in the marketing authorization for critically ill patients hospitalized in the intensive care unit (ICU) with an increased distribution volume or for patients on dialysis. Minichmay *et al.* suggested using a decisional algorithm for the continuous administration of meropenem based on the glomerular filtration rate in ICU patients depending on bacterial MIC to avoid underdosing [28]. In such situations of ICU renal dialysis, the continuous administration of meropenem leads to steady state concentrations 10 times higher than the MIC with a critical point at 2 mg/l, just like for *Pseudomonas aeruginosa* [24]. However, imipenem/cilastatin or



meropenem dosage should not be adapted in patients with liver failure [1, 8]. Plasma concentrations of both of these antibiotics should always be measured in patients experiencing treatment failure, unstable patients or in specific patients (obese patients, undernourished patients, neonates, elderly patients, etc.).

As for stability after dilution, imipenem/cilastatin remains stable for 3 to 4 hours [29]. A 24-hour stability after dilution could be reached under specific conditions: dilution in normal saline or 5% glucose solution with a final concentration <2.5 mg/ml, and storage in a glass vial at a temperature of 4°C kept away from direct light [30]. The use of elastomeric infusers for imipenem/cilastatin administration at home is therefore not recommended.

Meropenem remains stable for six hours and can reach 17 hours in polyvinyl chloride (PVC) syringes at maximum concentrations of 22 mg/ml diluted in normal saline solution and kept at room temperature (23°C) away from direct light. Higher stability could be reached if the solution were to be kept at 4°C [31-34]. Meropenem can thus be administered by continuous or long infusion. Similarly, the use of elastomeric infusers at home is possible with dilutions <5 mg/ml at room temperature (24°C) and away from direct light [35].

Concentrations obtained in various tissues vary depending on dosages and administration modes (short or long infusion) [2,19,36-50]. Variations are also observed from one patient to another and tissue concentration may be insufficient for bacteria with a MIC >1 mg/l (Table 5).

Imipenem/cilastatin and meropenem have a strong post-antibiotic effect on Gram-negative bacilli, from two to four hours for *Escherichia coli* and from four to six hours for *Pseudomonas aeruginosa* [1, 8]. Their ability to inhibit bacterial growth despite concentrations below the MIC distinguishes them from other beta-lactams. They are

therefore closely related to concentration-dependent antibiotics [8]. The administration mode is therefore believed to promote the time- or concentration-dependent nature of such antibiotics, especially in situations with high risks of underdosing (increased volume of distribution). Short infusions of high doses should therefore be preferred [8], especially for *Pseudomonas aeruginosa* infections.

## **6- Adverse effects**

Tolerability to carbapenems is similar to other beta-lactams.

Allergies account for less than 3% of all allergic risks to beta-lactams [1], but cross allergy with penicillin is estimated at 47% [51]. However, class allergy is not systematic. Lakhali *et al.* demonstrated the absence of cross allergic reaction between imipenem and meropenem [51]. Structural differences between these two molecules lie in their side chains; hence the hypothesis of a different involvement of such chains in allergic reactions. Meropenem is therefore not contraindicated in patients presenting with delayed hypersensitivity to imipenem/cilastatin [51]. This phenomenon could be explained by side chains recognizing T cells, and thus decreasing the likelihood of cross reactivity [51].

Common adverse effects such as pain at the injection site, skin rash, digestive disorders (nausea, vomiting, diarrhea) or even transitory metabolic disorders such as increased liver enzyme levels, increased creatinine blood levels, or increased urea levels, or hematological disorders (thrombocytosis, eosinophilia) may be observed. They all disappear at treatment discontinuation.

The main difference between these two molecules lies in the risk of neurological disorders. Imipenem/cilastatin has a convulsant action due to the basicity of its chain in C2 on the

gamma-aminobutyric acid receptors [3]. Risk factors for this complication are renal failure and an underlying neurological disease. Frequency of convulsions during treatment with imipenem/cilastatin is dose-dependent: from 0.5% to 1% for doses of 500 mg every six hours and up to 10% for doses of 1,000 mg every six hours [52,53]. Frequency of convulsions during treatment with meropenem is low (0.38%) [54].

The impact of penems on the gut flora is difficult to assess. The exponential use of antibiotics contributes to the emergence of resistance. Due to its alteration, the role of the gut flora in this resistance process has been clearly identified as a key point [55, 56].

There is a risk of bacterial resistance to carbapenems as soon as the first administration of imipenem/cilastatin [57]. Nord *et al.* performed a study in 10 patients who received imipenem/cilastatin for at least 11 days. They observed a decreased concentration of Enterobacteriaceae, enterococci, and anaerobic cocci with complete restoration of the gut flora after antibiotic discontinuation [58]. Kager *et al.* reported the complete disappearance of Enterobacteriaceae within the first three days of an antibiotic therapy with imipenem/cilastatin [59]. However, other studies reported the stability of the Enterobacteriaceae population but an increased concentration of enterococci and *Candida* spp. [60-62]. The impact on anaerobic bacteria is even more uncertain as several studies reported the stability of such flora [60-62], while another study reported its disappearance [59].

Very few studies have been performed on the impact of meropenem. A study [63] of 10 men receiving 500 mg of meropenem every 8 hours for 7 days reported i) a decreased concentration of Enterobacteriaceae, streptococci, *Clostridium* spp., and *Bacteroides* spp., ii) an increased concentration of enterococci, iii) no modification in the concentration of

staphylococci, micrococci, corynebacteria, yeasts, cocci, and anaerobic bacteria. Normalization was also observed two weeks after treatment discontinuation [63].

However, imipenem/cilastatin is believed to act as a potent inducer of ESBLs while meropenem is believed to act as a weak inducer [9].

## **7- Penems and specific populations**

### **a- Penems and pregnancy [64]**

As imipenem/cilastatin is an older molecule, more data sets are available and do not demonstrate malformations in newborns if women received such treatment during pregnancy. However, there is no data related to the use of such molecule during the first trimester of pregnancy.

Physiological modifications related to pregnancy (increased volume of distribution and glomerular filtration rate, especially with hydrophilic antibiotics) lead to adapting doses of imipenem/cilastatin, especially as non-renal elimination is suspected during pregnancy [65].

Following a 500-mg infusion of imipenem/cilastatin over 20 minutes every 8 hours, mean plasma concentrations are 14.7 +/- 4.9 µg/ml at the start of pregnancy and 14.9 +/- 5.2 µg/ml at the end of pregnancy, versus 43 +/- 28.3 µg/ml in non-pregnant women [65].

Concentrations of imipenem/cilastatin in the amniotic fluid vary during pregnancy, ranging from 0.07 +/- 0.01 to 0.72 +/- 0.85 µg/ml between the start and the end of pregnancy [65].

However, no accumulation of imipenem/cilastatin has been observed in infants born at term [65], despite slow elimination of approximately 3% after a 500-mg infusion over 30 minutes [65].

Less than 1% of the pediatric dose is found in breast milk during breastfeeding [64]. Cilastatin is not detected in breast milk [64].

Although data related to meropenem is scarcer, the absence of worrying data leads to allowing its use in pregnant and breastfeeding women [64].

#### b- Carbapenems and pediatrics

Imipenem/cilastatin and meropenem have similar pharmacokinetic properties in the pediatric population, with age-related variations. The elimination half-life in premature newborns is longer (increase of 1.5 hours approximately [66]), while it is similar to adults in children aged above 2 years with pharmacokinetic properties considered linear for dosages between 10 and 40 mg/kg [67]. However, the American Food and Drug Administration considers that meropenem should rather be used and contraindicates the use of imipenem/cilastatin in children with meningitis, because of milder neurological adverse effects with meropenem [67-69].

Adverse effects of meropenem only occur in 1% of children and present as diarrhea in 4.5% of cases (other gastrointestinal events are rarely observed) and skin rash in 2.2% of cases [67].

The use of meropenem in infants as young as 1 month at a dosage of 10 to 20 mg/kg/8hrs leads to clinical response in 98% of cases versus 93% with third-generation cephalosporin-based antibiotic regimens for severe bacterial infections [19]. Bacterial eradication in this group of patients reaches 97% versus 89% in the comparative treatment [19]. The recommended dosage of meropenem for children presenting with meningitis (3 months to 12 years) is 40 mg/kg/8hrs [19].

Similar to ICU adult patients, renal dialysis in children may modify the pharmacokinetic properties of antibiotics and lead to insufficient plasma concentrations. Dosages of 20 mg/kg as 30-minute infusion every 12 hours in children aged above 5 years lead to minimum concentrations of 4 mg/l at the end of a 12 hour-cycle [23].

Considering all these pharmacokinetic parameters, the recommended dosage in newborns and children aged 3 months to 12 years and weighing less than 50 kg is 10 to 40 mg/kg by the IV route every 8 hours (dosing adaptation takes into consideration the type and severity of infection, as well as the susceptibility of the bacterial agent) [67].

The recommended dosage for children presenting with febrile neutropenia is 20 mg/kg administered every 8 hours. Dosage is increased to 40 mg/kg for children presenting with cystic fibrosis or meningitis [67].

The use of meropenem in newborns seems to be associated with a significant decrease in diversity of the gut flora [70]. However, as a maturing process of the gut flora occurs following birth, any disturbance may lead to dysbiosis leading to an increased risk of some diseases such as necrotizing enterocolitis or late septicemia [69].

## **Conclusion**

Carbapenems are last resort molecules. Prescription options in hospital settings are either imipenem/cilastatin or meropenem. Although imipenem/cilastatin seems to have several advantages (especially in terms of activity against enterococci), the use of meropenem seems best for common indications. The action sought with the use of penems in routine clinical practice is the bactericidal action against Gram-negative bacilli and not against Gram-positive cocci.

Meropenem is therefore preferred because of its better intrinsic activity against Gram-negative bacilli, maximized by the possibility of using higher doses because of the lower neurological toxicity (Table 6).

Consequences of these two molecules on the gut flora in the mid and long term should be further assessed.

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**FIGURE**

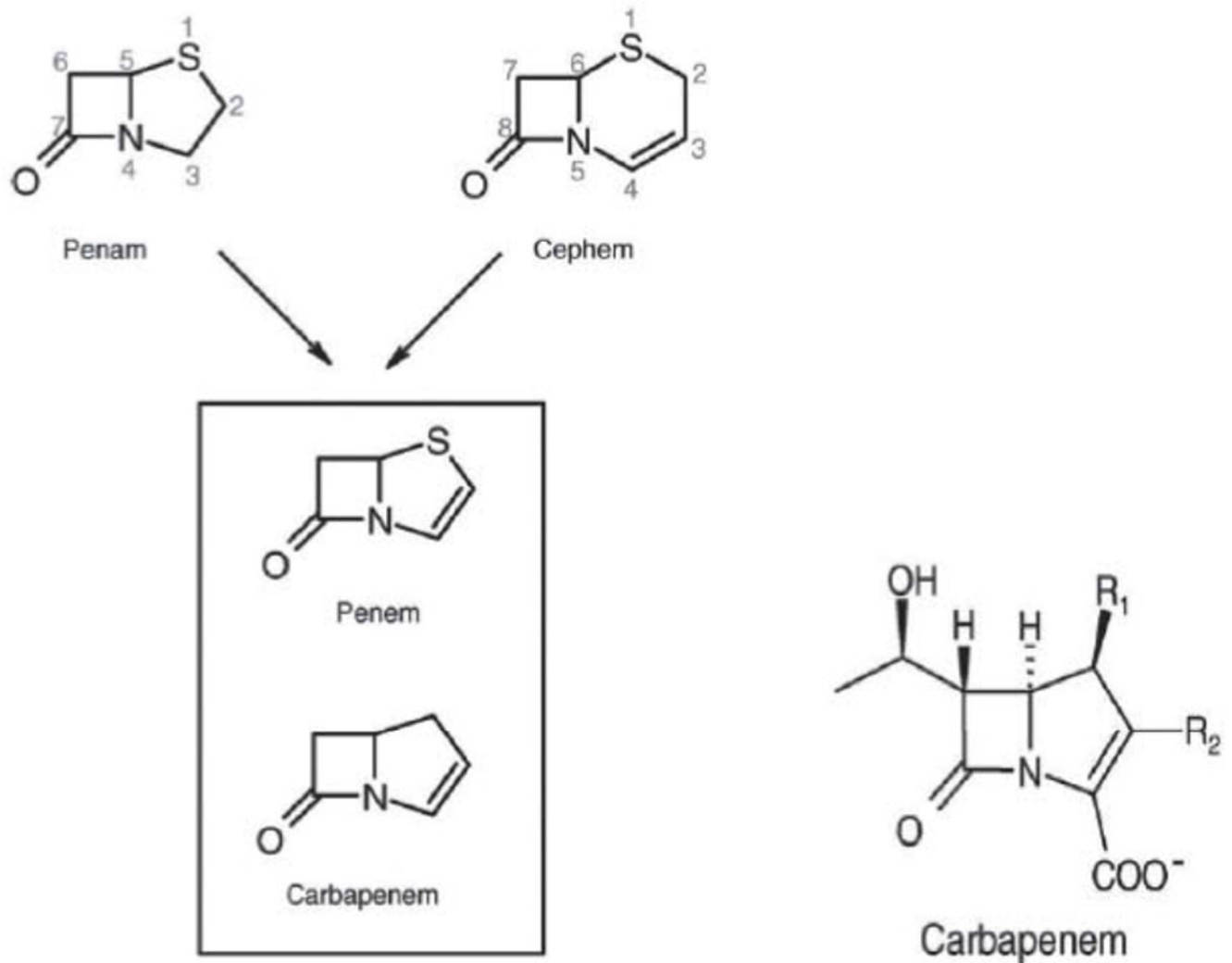


Figure 1 : Structure des carbapénèmes



**Tableau 1.** Activité in vitro de l'imipénème/méropénème sur les bactéries à Gram négatif [d'après 2, 9-18]

**Table 1.** In vitro activity of imipenem/meropenem on Gram-negative bacteria [from 2, 9-18]

Bacteria	imipenem		meropenem	
	MIC 50	MIC 90	MIC 50	MIC 90
<i>A. baumannii</i>	0.25	0.25	0.25	1
<i>C. freundii</i>	1	1	0.03	0.06
<i>E. coli</i>	0.12	0.25	0.016	0.03
ESBL-producing <i>E. coli</i>	0.25	0.5	0.03	0.06
<i>E. cloacae</i>	0.5	2	0.03	0.06
<i>H. influenzae</i>	0.5	1	0.12	1
<i>K. pneumoniae</i>	0.06	1	0.03	0.12
ESBL-producing <i>K. pneumoniae</i>	0.25	1	0.03	0.12
<i>M. catarrhalis</i>	0.06	0.12	0.008	0.015
<i>M. morgani</i>	2	8	0.12	0.25
<i>Prevotella</i> spp.	0.03	0.5	0.12	0.25
<i>P. mirabilis</i>	0.5	2	0.06	0.06
<i>P. aeruginosa</i>	1	>8	0.5	16
<i>Salmonella</i> spp.	≤0.5	≤0.5	0.03	0.03
<i>S. marcescens</i>	1	2	0.06	0.12
<i>Shigella</i> spp.	0.5	0.5	0.03	0.3
<i>S. maltophilia</i>	>8	>8	>16	>16

**Tableau 2.** Activité in vitro de l'imipénème/méropénème sur les bactéries anaérobies négatif [d'après 2, 9-18]

**Table 2.** In vitro activity of imipenem/meropenem on Gram-negative anaerobic bacteria [from 2, 9-18]

Bacteria	imipenem		meropenem	
	MIC 50	MIC 90	MIC 50	MIC 90
<i>B. fragilis</i>	0.25	1	0.12	1
<i>C. difficile</i>	2	4	2	4
<i>C. perfringens</i>	0.06	0.12	<0.06	<0.06
<i>Fusobacterium</i> spp.	0.12	1	0.12	0.25
<i>Peptostreptococcus</i> spp.	0.03	0.06	0.03	0.12
<i>Lactobacillus</i> spp.	0.12	8	0.25	>16

**Tableau 3.** Activité in vitro de l'imipénème/méropénème sur les bactéries à Gram positif [d'après 2, 9-18]

**Table 3.** In vitro activity of imipenem/meropenem on Gram-positive bacteria [from 2, 9-18]

Bacteria	imipenem		meropenem	
	MIC 50	MIC 90	MIC 50	MIC 90
<i>E. faecalis</i>	1	4	4	8
<i>E. faecium</i>	>8	>8	>16	>16
<i>L. monocytogenes</i>	0.03	0.12	0.12	0.12
Methicillin-susceptible <i>S. aureus</i>	0.06	0.06	0.12	0.12
Methicillin-resistant <i>S. aureus</i>	R	R	R	R
Methicillin-susceptible <i>S. epidermidis</i>	0.016	0.016	0.12	0.12
<i>S. agalactiae</i>	0.016	0.016	0.03	0.06
<i>S. pneumoniae</i> (susceptible to penicillin)	≤0.06	≤0.06	≤0.015	≤0.015
<i>S. pneumoniae</i> (resistant to penicillin)	0.5	1	0.5	1
<i>S. pyogenes</i>	≤0.008	≤0.008	≤0.008	0.08

**Tableau 4.** Propriétés pharmacocinétiques [d'après 1-3, 19-25]

**Table 4.** Pharmacokinetic properties [from 1-3, 19-25]

Properties	imipenem/cilastatin	meropenem
Bioavailability (IM)	60-75%	Missing data
C <sub>max</sub>	40 mg/l	49 mg/l
T <sub>max</sub>	1 hour	1 hour
T <sub>1/2</sub>	1 hour	1 hour
T <sub>1/2</sub> renal failure	3-4 hours	7-10 hours
Distribution volume in ICU patients	0.23-0.31 l/kg 0.25-0.57 l/kg	0.23-0.35 l/kg 0.30-0.48 l/kg
AUC:		
- 500 mg	42 mg.h/l	27-32 mg.h/l
- 1,000 mg	186 mg.h/l	67-77 mg.h/l
Protein binding	15-25%	2%
Unchanged renal excretion	70%	70%
Renal clearance (1 g)	130 ml/min/1.73 m <sup>2</sup>	176 ml/min/1.73 m <sup>2</sup>
Hemodialysis clearance	54.8% (imipenem) 62.9% (cilastatin)	50-70%
Hemofiltration clearance	30-50%	40-50%

IM: Intramuscular, ICU: intensive care unit, AUC : area under the curve

**Tableau 5.** Distribution tissulaire [d'après 2,19, 36-50]**Table 5.** Tissue distribution [from 2.19, 36-50]

	imipenem	meropenem
<b>Abdominal organs</b>		
Colon	8 mg/l (1,000 mg)	0.65-4.52 mg/l (1,000 mg)
Biliary fluid	10.5/13.5 mg/l (500/1,000 mg)	9.72 +/- 3.54 mg/l (1,000 mg)
Pancreas	3.35 mg/l (1,000 mg)	6.56 mg/l (1,000 mg)
<b>Genitourinary organs</b>		
Prostate secretions	1-2 mg/l (500 mg)	
Prostate tissue	5.3 mg/kg (500 mg)	2.96/7.09 µg/g (250/500 mg)
Cervix		8.5 µg/g (500 mg)
Endometrium		2.3 µg/g (500 mg)
Myometrium		3.6 µg/g (500 mg)
Ovaries		2.3 µg/g (500 mg)
Fallopian tubes		1.9 µg/g (500 mg)
Uterus		2.3 µg/g (500 mg)
Renal cortex	16-79 mg/kg (500 mg)	
Renal medullary	14-102 mg/kg (500 mg)	
<b>Chest organs</b>		
Pericardic fluid	10.5 mg/l (1,000 mg)	
Alveolar cells		5 mg/l (500 mg)
Bronchial mucus		3-13.3 mg/kg (1,000 mg)
Pleura		0.6-7.8 mg/l (1,000 mg)
Lung	0.28 mg/kg (1,000 mg)	0.2-8 mg/kg (1,000 mg)
<b>Eyes</b>		
Aqueous humor	5.2 mg/l (1,000 mg)	1.1 to 13.4 mg/l (2,000 mg)
Vitreous humor	0.2/2 mg/l (500/1,000 mg)	1.08 to 8.94 mg/l (2,000 mg)
<b>Nervous system</b>		
Cerebrospinal fluid (healthy patient)	0.6-0.9 mg/l (1,000 mg)	0.3-6.5 mg/l (1,000 mg)
Cerebrospinal fluid (meningitis)	1.1-2.3 mg/l (1,000 mg)	2.4/2.8 mg/l (1,000/2,000 mg)
<b>Muscular and bone and joint tissues</b>		
Muscles (except for ICU patients)	12.8 mg/l (500 mg)	
Muscles (ICU patients)	2.3 mg/l (500 mg)	
Subcutaneous tissues (except for ICU patients)	10.7 mg/l (500 mg)	
Subcutaneous tissues (ICU patients)	2.3 mg/l (500 mg)	
Joint fluid	7.9 mg/l (500 mg)	20.3 mg/l (500 mg)
Bone tissue	4.3 mg/kg (500 mg)	18.2 µg/g (500 mg)

Note: (500 mg/1,000 mg = penem doses)

**Tableau 6.** Principales différences imipénème-cilastatine/méropénème

**Table 6.** Main differences between imipenem-cilastatin and meropenem

	imipenem/cilastatin	meropenem
<b>Spectrum of activity</b>		
- Gram-positive cocci	↗	↘
- Gram-negative bacilli	↘	↗↗
<b>Pharmacokinetics</b>		
- Protein binding	↗	↘
- Stability after dilution	↘↘	↗↗
<b>Adverse effects</b>	↗↗	↘
<b>Impact on the gut flora</b>	= ?	= ?
<b>Daily cost</b>	=	=

Note: = no difference; ↗ higher than; ↘ lower than; = ? no difference but current data is not sufficient to conclude