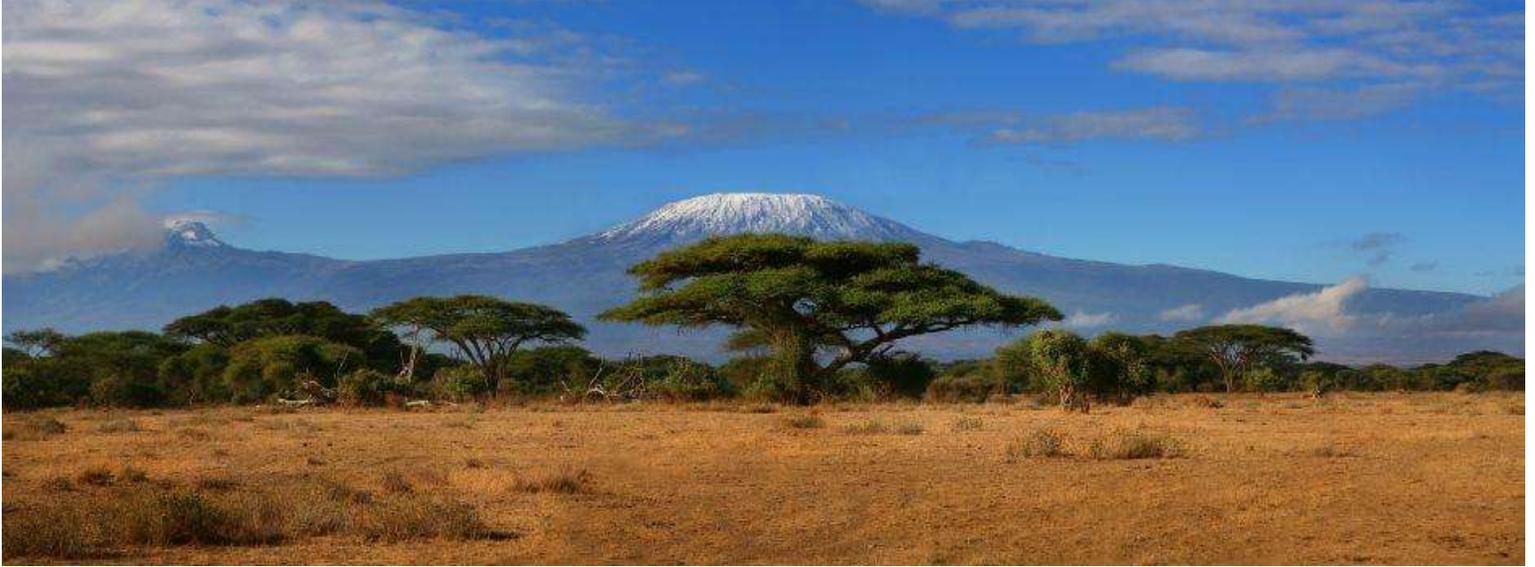


MEROPENEM



*Gregory Peck and Susan Hayward in the "Snows of Kilimanjaro"
(Twentieth Century Fox, 1952).*

"You're not going to die".

"Don't be silly. I'm dying now. Ask those bastards." He looked over to where the huge, filthy birds sat, their naked heads sunk in the hunched feathers. A fourth planed down, to run quick-legged and then waddle slowly toward the others.

“They are around every camp. You never notice them. You can’t die if you don’t give up.” ...

...He lay then and was quiet for a while and looked across the heat shimmer of the plain to the edge of the bush. There were a few Tommies that showed minute and white against the yellow and, far off, he saw a herd of zebra, white against the green of the bush. This was a pleasant camp under big trees against a hill, with good water, and close by, a nearly dry water hole where sand grouse flighted in the mornings.....

... He looked at her face between him and the fire. She was leaning back in the chair and the firelight shone on her pleasantly lined face and he could see that she was sleepy. He heard the hyena make a noise just outside the range of the fire.....

“Never believe any of that about a scythe and a skull,” he told her. “...it can have a wide snout like a hyena.” It had moved up on him now, but it had no shape any more. It simply occupied space.

“Tell it to go away.” It did not go away but moved a little closer.

“You’ve got a hell of a breath,” he told it. “You stinking bastard.”

It moved up closer to him still and now he could not speak to it, and when it saw he could not speak it came a little closer, and now he tried to send it away without speaking, but it moved in on him so its weight was all upon his chest, and while it crouched there and he could not move or speak, he heard the woman say, “Bwana is asleep now. Take the cot up very gently and carry it into the tent.”....He could not speak to tell her to make it go away and it crouched now, heavier, so he could not breathe. And then, while they lifted the cot, suddenly it was all right and the weight went from his chest....

It was morning and had been morning for some time and he heard the plane. It showed very tiny and then made a wide circle and the boys ran out and lit the fires, using kerosene, and piled on grass so there were two big smudges at each end of the level place and the morning breeze blew them toward the camp and the plane circled twice more, low this time, and then glided down and leveled off and landed smoothly and, coming walking toward him, was old Compton in slacks, a tweed jacket and a brown felt hat...It was difficult getting him in, but once in he lay back in the leather seat, and the leg was stuck straight out to one side of the seat where Compton sat. Compton started the motor and got in. He waved to Helen and to the boys...

...Then they were over the first hills and the wildebeeste were trailing up them, and then they were over mountains with sudden depths of green-rising forest and the solid bamboo slopes, and then the heavy forest again, sculptured into peaks and hollows until they crossed, and hills sloped down and then another plain, hot now, and purple brown, bumpy with heat and Compie looking back to see how he was riding. Then there were other mountains dark ahead.

And then instead of going on to Arusha they turned left, he evidently figured that they had the gas, and looking down he saw a pink sifting cloud, moving over the ground, and in the air, like the first snow in a blizzard, that comes from nowhere, and he knew the locusts were coming, up from the South. Then they began to climb and they were going to the East it seemed, and then it darkened and they were in a storm, the rain so thick it seemed like flying through a waterfall, and then they were out and Compie turned his head and grinned and pointed and there, ahead,

all he could see, as wide as all the world, great, high, and unbelievably white in the sun, was the square top of Kilimanjaro. And then he knew that there was where he was going....

Just then the hyena stopped whimpering in the night and started to make a strange, human, almost crying sound. The woman heard it and, stirred uneasily. She did not wake. In her dream she was at the house on Long Island and it was the night before her daughter's debut....Then the noise the hyena made was so loud she woke and for a moment she did not know where she was and she was very afraid. Then she took the flashlight and shone it on the other cot that they had carried in after Harry had gone to sleep. She could see his bulk under the mosquito bar but somehow he had gotten his leg out and it hung down alongside the cot. The dressings had all come down and she could not look at it.

"Molo," she called, "Molo! Molo!"

Then she said, "Harry, Harry!" Then her voice rising, "Harry! Please. Oh Harry!"

There was no answer and she could not hear him breathing.

Outside the tent the hyena made the same strange noise that had awakened her. But she did not hear him for the beating of her heart.

Ernest Hemingway , "The Snows of Kilimanjaro", 1936.

Harry and his immensely wealthy wife, Helen, have been stranded on the simmering great plains at the foot of Mount Kilimanjaro, the tallest mountain in all of Africa. Just as the ancient Greeks revered Mount Olympus and the ancient Hebrews revered Mount Sinai, the local Masai revered Kilimanjaro and they called it the "House of God". Harry and Helen had been on safari in eastern Africa, and when their vehicle disastrously broke down many many miles from civilization - the chances of rescue appeared remote. The situation had become even worse, as Harry had developed a life threatening gangrene in his leg as the result of an infected thorn wound which he had sub optimally treated far too late with carbolic acid instead of using iodine. In the heat, the smell of his gangrenous leg has become unbearable, and because of this he suspects that he may die, before a rescue plane can arrive. His wife tries to reassure him, but he stoically points out the circling vultures overhead, horrible creatures who can smell death from across vast distances.

As he becomes more unwell he drifts in and out of an agitated delirium, during each vivid dreamlike episode reliving dramatic parts of his past life. We was, or at least he was going to be, a very great writer, and he had many stories from his adventurous life, stored in his mind that he had intended to use as the basis for his future literary works. But now he regrets that this will never happen, and he becomes increasingly bitter that he has wasted his life. He had been attracted to a series of wealthy women, whom in turn had been attracted to the handsome, glamorous and adventurous writer. He now realizes that by becoming the plaything of wealthy widows and divorcees, he had chosen a life of ease and comfort that had had the effect of completely killing off his genius and latent literary genius. He is not a terribly attractive character, seeming to dislike women, even though they have provided for his material comfort. He now blames them for suffocating his true love and talent, which was writing. He is cruel to Helen, whom he does not love, yet she loves him very much. Helen tries to feed him broth to keep up his strength, but he wants only to drink whiskey. Helen even goes off by herself and kills some game for their dinner, but still he will not eat. Instead they both set to drinking whiskey. He

comes to see that Helen is a good woman and admires her strong weathered features by the light of the campfire. He tells her that despite all the other women he had had he does in fact love her and he regrets their tempestuous relationship.

Helen lovingly dresses his wound, despite the unpleasantness of the task. The infection is rapidly spreading and Harry repeatedly apologizes for its now appalling stench. He feels death creeping ever closer, despite Helen's frantic reassurances, and in his mind he sees death not as the traditional reaper with scythe, but rather in the local traditions of its sinister African guise of the vulture and the hyena. He likens the creeping gangrene to the hyena that creeps around the edges of their camp by night, with its other worldly almost human like screeches. Suddenly he feels the hyena is upon his chest and he struggles for breath. But then it seems to him it is suddenly morning and his friend Compton has dramatically arrived in his plane just in the nick of time to save him. There is only room for one passenger in the plane, and Helen insists that Compton takes Harry first. In the plane Harry's trip appears surreal. It's as if he is travelling through great forests, over immense herds of wild running animals and even through vast waterfalls - all the images of Africa are crowding into his fevered mind at once. Compton, turns to him from the cockpit, smiling and points out of the window. He turns and sees the brilliant white snows of Mount Kilimanjaro, and realizes then that that is his destination.

The hyena gives a terrible primal howl, and wakens Helen suddenly from her dream in which she was back home safely with her family, though some kind of argument was occurring. She instinctively glances towards Harry's cot, where she sees his limp body. She cannot detect any sign of breathing. The sound of her pounding heart drowns out the distant wails of the hyena.

Even if Harry had made it back to civilization, he may not have survived in 1936, (though happily Gregory Peck does so in the movie version). The surgeon's knife remains the best option for gangrene, but the greatest chance of survival comes with the additional use of one of the biggest guns in the 21 century arsenal of antibiotics - meropenem.



Frontispiece illustration from the original publication, of Ernest Hemingway's, "The Snows of Kilimanjaro", 1936.

MEROPENEM

Introduction

Meropenem is a **carbapenem** antibiotic.

Carbapenems have the **broadest spectrum** of all the antibacterial classes, with good activity Gram-positive organisms and Gram-negative organisms (including extended activity against many resistant strains of Gram-negative organisms) and anaerobes.

The widespread use of carbapenems has been linked with increasing prevalence of infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci (VRE), multiresistant Gram-negative organisms and *Clostridium difficile*.

Their use therefore is usually reserved for **serious / life threatening infections**.

Meropenem has several advantages over imipenem, including:

- Imipenem may be inactivated by a renal dipeptidase enzyme. Imipenem therefore is usually formulated in combination with a dipeptidase inhibitor, cilastatin.
- Meropenem attains higher concentrations in the CSF.
- Meropenem has a lower incidence of seizure complications than imipenem.

History

When the first bacterial beta - lactamases emerged in the late 1960s, and reduced the efficacy of the penicillins, an intensive search for both beta - lactamase inhibitors and beta - lactamase resistant antibiotics was launched.

The carbapenem antibiotics were originally developed from the carbapenem thienamycin, a natural substance derived from the gram positive bacterium, *Streptomyces cattleya*.

Imipenem/cilastatin was introduced in 1985.

Meropenem was introduced in 1996.

Ertapenem was introduced in 2001.

Chemistry

The **beta-lactam antibiotics** are structurally related via their central **beta lactam** moiety.

Side chains determine antibacterial, pharmacological and pharmacokinetic properties.

The beta-lactam antibiotics include:

1. Penicillins

2. Cephalosporins
3. Carbapenems
4. Monobactams

The carbapenems have a particular chemical structure that renders them highly resistant to most beta-lactamases

Classification

The carbapenem antibiotics include:

- Imipenem
- Meropenem
- Ertapenem

Preparations

Ampoules: 500 mg, 1 gram (as powder for reconstitution).

Mechanism of Action

The carbapenem antibiotics are **bactericidal** agents.

They interfere with **bacterial cell wall peptidoglycan** synthesis during the stage of active multiplication, thereby leading to cell lysis and death.

Carbapenems have the broadest spectrum of all the antibacterial classes, with good activity against Gram-negative and Gram-positive organisms and anaerobes.

They are resistant to hydrolysis by most beta-lactamases including extended-spectrum beta-lactamases (ESBLs)

However, Gram-negative organisms with acquired ability to produce metallo-beta-lactamases (carbapenemases) often inactivate all beta-lactams except aztreonam.

Pharmacodynamics

Meropenem and **imipenem** have very broad activity including:

- Many Gram-positive organisms
 - ♥ Including *Nocardia* species
 - ♥ However inactive against MRSA
- Gram-negative organisms:

- ♥ Including isolates producing extended-spectrum beta-lactamase enzymes (ESBLs)
- ♥ *Pseudomonas aeruginosa* (comparable to that of aminoglycosides).
- ♥ Imipenem has useful clinical activity against *Enterococcus faecalis*, which meropenem lacks.
- Anaerobic organisms:
 - ♥ There is excellent activity against these including *Bacteroides fragilis*.

Carbapenem resistance is emerging worldwide, often due to the production of various **carbapenemase** enzymes, which also confer resistance to other antibiotics.

Pharmacokinetics

Absorption:

- Meropenem is administered intravenously.

Distribution

- Meropenem penetrates well into most body fluids and tissues including cerebrospinal fluid of patients with bacterial meningitis, achieving concentrations in excess of those required to inhibit most bacteria.
- Plasma protein binding of meropenem is low at approximately 2%.

Metabolism and excretion:

- About 70 % of meropenem is excreted unchanged in the urine.
- About 30 % is metabolized by the liver to a single inactive metabolite.
- In subjects with normal renal function, meropenem's elimination half-life is approximately one hour.

Indications

Meropenem may be used in serious / life-threatening infections including:

1. UTIs
2. Intra-abdominal infections
3. Lower respiratory tract infections.
4. Meningitis:

- Meropenem is effective in treating meningitis.

Imipenem is contraindicated in meningitis due to its epileptogenic potential; however, if it is used carefully the difference in this potential between imipenem and meropenem is small.

5. Febrile neutropenia
6. Necrotizing soft tissue infection / gangrene, (often in combination with other agents):
 - Severe mixed aerobic and anaerobic infections, particularly when combinations with an aminoglycoside are contraindicated
7. Melioidosis, (usually in combination with other agents)
8. Septicaemia.

Note that, as for all antibiotics, the prevalence of bacterial resistance may vary geographically and over time for selected species and local information on resistance is also important, particularly when treating severe infections.

Contra-indications/precautions

These include:

1. Contraindicated with a history of severe or immediate allergic reaction to meropenem.
2. Caution in those with a history of an allergic reactions to other beta lactam antibiotics:
 - As cross-reactivity between penicillins, cephalosporins and carbapenems can occur.

Pregnancy

Meropenem is classified as a B2 drug with respect to pregnancy.

Category B2 drugs are those drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals are inadequate or may be lacking, but available data show no evidence of an increased occurrence of fetal damage.

Breast feeding

Safe in breast feeding

Adverse Effects

All the beta lactams including the carbapenems have a **wide therapeutic index** and are not associated with significant adverse effects, apart from hypersensitivity reactions..

Adverse reactions include:

1. GIT upset, (as with most antibiotics).
2. Allergic reactions;
 - Including serious and *fatal* **anaphylactic** reactions.

Anaphylaxis is more frequent following **parenteral** therapy, but it has also occurred in patients on oral therapy
3. Dermatological:
 - Occasionally severe reactions such as Stevens-Johnson syndrome.
4. Pseudomembranous colitis:
 - Pseudomembranous colitis has been reported with nearly all antibacterial agents, including the cephalosporins, and may range in severity from mild to life-threatening.

Therefore, it is important to consider this diagnosis in patients who present with diarrhoea subsequent to the administration of antibacterial agents.
5. Neurotoxicity:
 - Imipenem is associated with neurotoxicity (myoclonic activity, confusion and seizures), especially when excessive doses are used in people with CNS disorders (e.g. history of seizures) or renal impairment.

Ertapenem is also associated with seizures, especially in those with CNS disorders or renal impairment.

Meropenem has the least neurotoxicity of the carbapenems.

Dosing

Exact dosing and the duration of dosing depends on the condition being treated as well as the severity of the condition and illness.

In *general* terms:

- **Meropenem 1 - 2 grams IV 8 hourly.**
- **Child: 25 - 50 mg/kg up to 2 grams IV**

See latest Antibiotic Therapeutic Guidelines for full prescribing details.

References

1. eTG Complete - March 2015.
 - Antibiotic Therapeutic Guidelines, 15th ed 2014.
2. Meropenem in Australian Medicines Handbook, accessed February 2015.
3. Meropenem in MIMs 1 September 2014.

Dr J. Hayes
Reviewed July 2015.