Journal of Bacteriology and Parasitology

Barrios, et al., J Bacteriol Parasitol 2014, 5:5
DOI: 10.4172/2155-9597.1000199

Review Article Open Access

A New Treatment Choice against Multi-Drug Resistant *Pseudomonas aeruginosa*: Doripenem

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Rec date: April 08, 2014; **Acc date:** September 19, 2014; **Pub date:** September 23, 2014

Abstract

Pseudomonas aeruginosa is a Gram-negative strict aerobic *Bacillus* that causes around 10% of nosocomial infections. This *bacillus* can become resistant to multiple antibiotics, and it has been described mainly in inmuno compromised patients. The prevalence of multidrug resistant *Pseudomonas* has been increasing over the last few years. Currently we have new agents to treat this type of infection. Doripenem is the new B-lactam from the carbapenem family, which has demonstrated in vitro the best activity against multidrug resistant *Pseudomonas aeruginosa* in different studies. Its mechanism of action consists of the inactivation of penicillin-binding proteins in the cell wall. This agent has been indicated in the treatment of several infections, such as complicated intra-abdominal infections, complicated urinary tract infections and nosocomial pneumonia. The principal difference between doripenem and the other carbapenems, is the capacity of preventing the generation of resistant strains of *Pseudomonas aeruginosa*, so it is especially useful for severe infections caused by multidrug resistant *Pseudomonas aeruginosa*. But this situation may change if we don't use antibiotics properly. Promoting rationale use of antibiotics to treat infections caused by *Pseudomonas aeruginosa* may be critical to make the emergence of multidrug resistant strains difficult. The present review describes the main features of doripenem and its potential role in managing infections due to multi-drug resistant *Pseudomonas aeruginosa*.

Keywords: Doripenem; Carbapenems; *Pseudomonas aeruginosa*; Multidrug-resistance; Nosocomial infection

Pseudomonas aeruginosa: Microbiological, Clinical and Epidemiological Features

Pseudomonas aeruginosa is a Gram-negative aerobic and facultative anaerobic *bacillus* which belongs to the Pseudomonadaceae family. It is a small microorganism, straight or slightly curved, non-fermenting glucose and not sporulated. It has motility due to a single polar flagellum and twitching. Its identification in the laboratory is simple, because the germ grows easily in a wide variety of media and the requirements for its identification are scarce. Most cultures of this bacteria produce a blue-green pigment pyocyanin; it is useful for identification of the microorganism, and because of the characteristic color of copper oxide, the bacteria is named *aeruginosa* [1].

This germ is typically associated with nosocomial infections, causing about 10% of infections acquired in the hospital, but community-acquired infections also contributes to a substantial number of cases [2,3]. *Pseudomonas* causes a variety of infections, mainly urinary tract infections, respiratory infections, ocular infections, endocarditis, bone and joint infections, burn infections and other skin infections, such as ecthyma gangrenosum or cellulitis.

These infections are often difficult to treat because the bacteria is sensitive to few antibiotics, and also can produce multiple resistance to other antibiotics during the infection treatment [4,5]. Using several classes of antibiotics to treat infections caused by this bacterium can lead to the emergence of new mutant strains, which have a high level of resistance to many antibiotics [6]. Multidrug-resistant (MDR) *Pseudomonas aeruginosa* has been described mainly in patients who are immunocompromised, or patients with cystic fibrosis or neoplastic diseases, or patients in Intensive Care Units [7-9].

The incidence rate of infections produced by MDR *Pseudomonas aeruginosa* strains may vary from 5.5 to 14 cases per 10,000 patients admitted per year [10,11]. A study developed in a hospital in Rome, Italy [12] revealed the first case of MDR *Pseudomonas aeruginosa* infection in a haematologic patient in 1992. After that, the prevalence of MDR *Pseudomonas aeruginosa* increased from 8% in 1993 to 17% in 1999, related to that hospital. Of 358 cases of bloodstream infections due to *Pseudomonas aeruginosa*, 14% (51 cases) were caused by strains of MDR *Pseudomonas aeruginosa*. In these cases, 96% (46 infections) were nosocomial.

The overall mortality rate due to *Pseudomonas aeruginosa* infection is greater than 20%, which increases when the infection is due to MDR *Pseudomonas aeruginosa* strains [10,12].

A New Therapeutic Weapon against Mdr *Pseudomonas aeruginosa*: Doripenem

Pharmacologic aspects of Doripenem

Doripenem (DPM) is the new β-lactamic from the carbapenems family. It has a four membered β-lactamics in one ring, which connect with a second ring in the structure [13], as shown in Figure 1. For the carbapenemic family the structure is based on a ring of 5 thiazolidinic membered in comparison with cefalosporines and thiazolidine, which

have 6 dihydrothiazine membered and 5 penicilins membered respectively. The trans-hydoxyethil group configurated in two positions in the principal ring of carbapenems provides protection to β-lactames enzymes, while the side chains present in the secondary ring contribute to the broad spectrum of activity and chemical stability [13-15].

The pharmacokinetics of DPM is linear over a dose range of 500 mg to 1 g when intravenously infused over 1 hour. There is no accumulation of DPM after several intravenous perfusions from 500 mg to 1 g taking each 8 hours during 7 to 10 days in patient with normal kidney function (Figure 2). The DPM average union to plasmatic proteins is approximately 8.1% and it is independent from the plasmatic concentration. The median volumen of distribution at steady state is 16.8 litres (range: 8.09-55.5 litres). In healthy patients, it is similar to extracellular liquid volume (18.2 litres) [16].

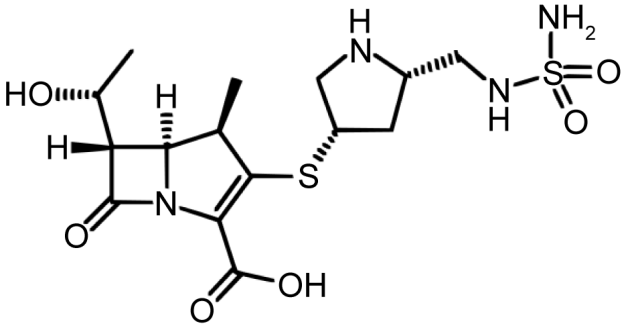

Figure 1: Chemical structure of doripenem.

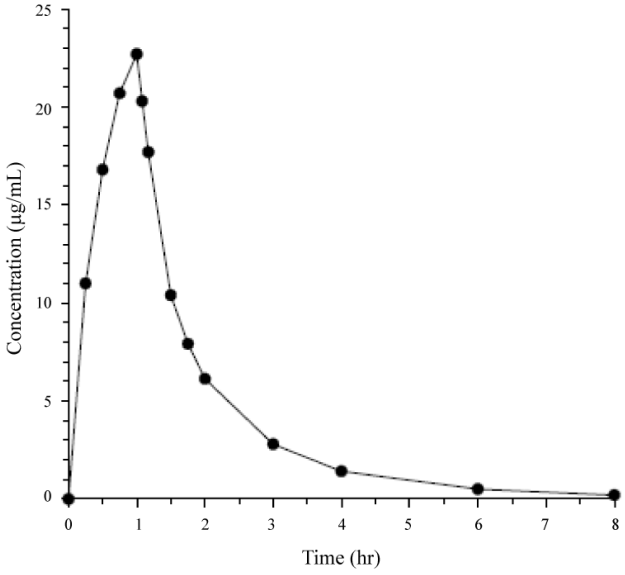

Figure 2: Average doripenem plasma concentration versus time Following a single 1-hour intravenous infusion of 500 mg doripenem in healthy subjects

DPM penetrates into body fluids and several tissues, including infection places for the authorised indications [15] (complicated intra-abdominal infection, complicated urinary tract infection and nosocomial pneumonia). Concentrations of DPM in peritoneal and retroperitoneal fluids are equals or higher than the necessaries for the inhibiton of susceptibles bacterias, however, the clinical relevance of this point has not been stablished yet. The concentration reached in selected tissues is shown in Table 1.

Maximum concentration (mcg/ml)	23
Elimination half-life (hours)	1
Protein binding (%)	9
Renal excretion (%)	75
Stability at room temperature (hours)	4-12
MIC 50 against Pseud. aeruginosa (mcg/ml)	0.5
MIC 90 against Pseud. aeruginosa (mcg/ml)	8

Table 1: Pharmacologic properties of Doripenem. MIC: minimum inhibitory concentration

During metabolism of DPM, a metabolite of the open ring without microbiological activity is made by dehydropeptidase-I. Citocromo p450 (CYP450) has no activity or very low activity on the DPM metabolization. Kidneys eliminate DPM intact. The DPM plasmatic half-life elimination in young healthy adults is approximately one hour, and the plasmatic aclearment is 15.9 l/hour. The average of renal aclearment is 10.3 l/hour. The magnitude of this figure, with the notable decrease in the elimination of DPM observed when co-administered with probenecid, indicated that DPM undergoes glomerular filtration, tubular secretion and reabsorption. Young and healthy adults who received a single dose of 500 mg of DPM, recovered 71% of the dose as intact active and the 15% of the dose as a metabolite of the open ring [17].

The mechanism of action of DPM is performed by the interference of the bacterial wall biosynthesis, concretely inactivates essential penicillin-binding proteins (PBP) in the cell wall, due to structural analogy with dipeptide D-Ala-D-Ala, natural substract of PBP, inhibiting cell wall biosynthesis with the result of bacterial cell death. DPM has to go through the bacterial wall made by lipopolysacarids, which they do along the porin channels in gram negative bacteria. This characteristic gives the opportunity to keep active in the presence of activity inactivator of carbapenems enzymes [16].

Most common adverse events were: headache (10%) diarrhea (9%) and nausea (8%). The 0.1% of the patient interrupted the administration of DPM because the adverse event and they were: nausea (0.1%) diarrhea (9%) pruritus (0.1%) fulgar valvular (0.1%) and elevated liver enzymes (0.2%) [17].

The standard dosage of DPM is 500 mg/ 8 hours, regardless of the type and severity of infection [16]. Activity of DPM is time-dependent; that is why it is important to respect dosage intervals to achieve and to maintain optimal concentrations throughout time with the aim of obtaining the best possible therapeutics. In patients with moderate renal insufficiency (Clearment of creatinine [ClCr] 30-50 mL/min), the dosage of DPM should be 250 mg/8 hours [16,17]. Due to limited clinical data and an expected increase in exposure of DPM and its metabolite, it should be used with caution in patients with severe renal impairment. In patients with severe renal insufficiency (ClCr<30 mL/

min) the dosage should be 250 mg/12 hours. DPM is not recommended for hemodialyzed patients [14,15,18].

DPM studied in-vitro has shown more affinity for PBP, concretely PBP 2 and 3, in *Pseudomonas aeruginosa* comparatively with imipenem (IPM) [13]. Another study demonstrated the stability of DPM in the presence of several enzymes. DPM was also the most potent carbapenem for *Pseudomonas aeruginosa* (Minimum inhibitory concentration [MIC] 90 0.5 mg/L) in comparison with meropenem (MPM) (MIC 90 1 mg/L) and IMP (MIC 90 2 mg/L) [1]. All the isolates have the DPM MIC values 0,06 mg/L and the average incomes ertapenem (EPM) 1 mg/L [15].

Antibacterial activity and efficiency of DPM

The activity of DPM has been investigated recently for MDR gram negatives bacilli isolates from cystic fibrosis patient [18]. MDR was defined as the resistant to all the agents in at least two categories (quinolones, aminoglycosides y β-lactams). In general, 400 isolates of *Pseudomonas aeruginosa* (mucoide 200 and non-mucoide 200) and 200 Burkholderia cepacia isolates were investigated. DPM got the lowest CIM 50 and CIM 90 values for all the isolates compared with other 7 agents including MIP (MPM was not included). The authors concluded DPM has the best activity in vitro against MDR *Pseudomonas aeruginosa*. These results were supported by other additional data obtained from patient with or without cystic fibrosis [13].

Pseudomonas aeruginosa is natural way resistant to cefalosporine first and second generation, tetracyclines, chloranphenicol and macrolides. The strain can be transmitted between their genetic materials which gives the resistance, even to other gram negative bacteria such as enterobacteriae. Another factor is the capacity to become resistant during the antibiotic treatment. The Zinc, component of some urinary catheters, also induces molecular changes which activates imipenem resistance [19].

In the 10.2% of *Pseudomonas aeruginosa* treatments, it is evidenciated that appears a resistant strain, which was sensible before the treatment [16]. This induction of resistance fluctuates depending on the antibiotic used. IMP presents the highest induced resistance after the treatment. DPM has more capacity than the rest of the carbapenems to prevent the generation of *Pseudomonas aeruginosa* strain resistant. In nosocomial neumonia it was also superior than piperacillin/tazobactam for MDR pathogens, such as *Pseudomas aeruginosa*. In complicated intraabdominals infections, it was proved not to be inferior to MPM [17]. DPM has a lower number of indications than MPM, especially in Nervous Central System infections, where DPM is not indicated.

The main mechanism of resistance in *P. aeruginosa* is provided by β-lactamase and changes in membrane permeability given by the presence of efflux pumps and mutations of the transmembrane porins. [19] As a strategy for avoid a possible resistance to DPM we can use a infusion of MPM in 3 hours, continuous infusion of piperacillin/tazobactam, or continous infusion of Ceftazidima, or aztreonam if it is possible, or associated colistina+rifampicina by synergism [16].

Conclusions

Further research is needed in order to stablish the clinical relevance of DPM for treating intraabdominal infections caused by *Pseudomonas aeruginosa*, since concentrations in peritoneal and retroperitoneal fluid are equals or higher than the necessaries for the inhibiton of susceptibles bacterias.

The principal advantage of DPM is the higher activity against *Pseudomonas aeruginosa* than the rest of carbapenems, so it is especially useful for severe infections caused by MDR *Pseudomonas aeruginosa*. But this situation may change if we don't use antibiotics properly. Promoting rationale use of antibiotics to treat infections caused by *Pseudomonas aeruginosa* may be critical to make the emergence of MDR strains difficult.

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