http://www.revistanefrologia.com

short review

Intraperitoneal administration of daptomycin in recurrent peritonitis with suspected biofilm

Laura García-López[1], M. José Fernández-Reyes Luis[2], M. Teresa Criado-Illana[3], Leonor Gómez-Sayago[1], Manuel Heras-Benito[2]

[1] Servicio de Farmacia Hospitalaria. Hospital General de Segovia. Segovia (Spain)
[2] Servicio de Nefrología. Hospital General de Segovia. Segovia (Spain)
[3] Servicio de Farmacia Hospitalaria. Jefa de Servicio de Farmacia. Hospital General de Segovia. Segovia (Spain)

Nefrologia 2012;32(2):139-42
doi:10.3265/Nefrologia.pre2011.Nov.11066

ABSTRACT

Forms of peritonitis are the most problematic infections in patients undergoing peritoneal dialysis since they can jeopardise the technique. Current treatment includes administering vancomycin, cephalosporins and aminoglycosides empirically until the cause of the infection is known. However, the current situation with regard to emerging bacterial resistances makes it necessary to include new drugs in the therapeutic array for complicated forms of peritonitis that may become recurrent and compromise dialyser efficacy. Daptomycin is a lipopeptide antibiotic used to treat gram-positive bacterial infections. It has not yet been approved for treatment of infections of this type, but it is starting to be used in this area due to being highly effective against meticillin-resistant bacteria with intermediate sensitivity to vancomycin, particularly when the bacteria are associated with biofilm formation.

Keywords: Daptomycin. Intraperitoneal. Peritonitis. Peritoneal dialysis.

Administración intraperitoneal de daptomicina en peritonitis recurrente con sospecha de biofilm
RESUMEN

Las peritonitis son las infecciones más problemáticas en los pacientes sometidos a diálisis peritoneal, puesto que pueden llegar a comprometer la técnica. Actualmente el tratamiento incluye tratamiento empírico con vancomicina, cefalosporinas y aminoglucósidos hasta conocer el causante de dicha infección. Pero la realidad microbiológica, en cuanto a emergencia de resistencias, hace necesaria la incorporación de nuevos fármacos al arsenal terapéutico para tratar las peritonitis complicadas que pueden convertirse en recurrentes y comprometer la eficacia de la membrana. La daptomicina es un antibiótico lipopeptídico que se utiliza para el tratamiento de infecciones por bacterias grampositivas. No tiene aprobada la indicación en el tratamiento de este tipo de infecciones, pero está comenzando a utilizarse en este campo debido a su elevada efectividad ante infecciones por bacterias resistentes a meticilina con sensibilidades intermedias a vancomicina, sobre todo cuando se asocian a la presencia de un biofilm.

Palabras clave: *Daptomicina. Intraperitoneal. Peritonitis. Diálisis peritonel.*

According to recent treatment guidelines for peritonitis in patients undergoing peritoneal dialysis (PD), peritonitis accounts for approximately 18% of the infections associated with mortality in PD patients. Although less than 4% of peritonitis cases result in death, peritonitis is a factor contributing to exitus in 16% of all patients who die while on PD. Severe and long-lasting episodes of peritonitis may lead to peritoneal membrane failure. These episodes are one of the most common reasons for PD failure and one of the most common causes of discontinuing PD and starting haemodialysis. With these reasons in mind, prevention and treatment of PD-related peritonitis is crucial to the overall care of these patients. Episodes must be resolved as effectively as possible in order to preserve peritoneal membrane function and by extension the PD technique as well. Treatment should be initiated as quickly as possible,

Correspondence: Laura García López
Servicio de Farmacia Hospitalaria.
Hospital General de Segovia, Segovia. Spain
laugarcilo@yahoo.es
lgarcialo@saludcastillayleon.es

and must include gram-positive coverage with vancomycin or cephalosporins and gram-negative coverage with third-generation cephalosporins or aminoglycosides.[1]

Delivering antibiotics by the intraperitoneal (IP) route is more effective for treating PD-related peritonitis than administration by the intravenous (IV) route.

At present, the constant emergence of multidrug-resistant bacteria also affects this type of infection and results in new challenges in the treatment of this disease. Daptomycin may be a valid option for the treatment of infections caused by gram-positive bacteria with resistance to methicillin and intermediate sensitivity to vancomycin.

Daptomycin, discovered in the early 1980s, is a 13 amino acid lipopeptide antibiotic. Clinical development of the drug was halted at that time due to its lack of efficacy against endocarditis and its high toxicity, particularly to skeletal muscle. In recent years, the constant appearance of multidrug-resistant pathogens has led to renewed interest in this antibiotic, which was approved by the Food and Drug Administration (FDA) in 2003 for treating gram-positive infections.[2] Its 3 phase mechanism of action differentiates it from other antibiotics and, so far, has prevented bacteria from developing resistances.

In Spain, the drug has been officially approved for the treatment of complicated skin and soft tissue infections, right-sided endocarditis caused by *Staphylococcus aureus*, *Staphylococcus aureus* bacteraemia associated with right-sided endocarditis, and skin and soft tissue infections by the IV route only.

Dosage for the approved indications is 4-6mg/kg IV every 24 hours. In the presence of decreased renal function or creatinine clearance <30ml/min, it must be administered every 48 hours.

It only acts on gram-positive bacteria and it is not physically or chemically compatible with glucose, so it has to be diluted in saline in order to be administered by the IV route. Its activity is pH-independent. All of these properties, which will be discussed later, are very important in the context of PD-related peritonitis.

Very little evidence is currently available regarding use of daptomycin in the treatment of PD-related peritonitis.[2,3] Burklein D. et al[4] described the case of a patient with an intestinal perforation that led to peritonitis and sepsis that caused renal failure. Microbial testing revealed a strain of *Enterococcus faecium* that is only sensitive to vancomycin. Given the patient's renal function, IV daptomycin was administered in doses of 4mg/kg every 48 hours during the first 6 days. After recovering renal function, daptomycin was administered in the same quantities every 24 hours until completion of 14 days of treatment. IP and plasma daptomycin levels were measured, showing a maximum antibiotic concentration of 17mg/l and a minimum concentration of 5mg/l, which was sufficient considering that 4 mg/l is the minimum inhibitory concentration (MIC) of daptomycin against most enterococci.[2,3] In this case, peritonitis resolved successfully.

Dmyto K el al[5] published a case in which a patient on PD with recurrent peritonitis and suspected *Staphylococcus capitis* biofilm was administered IV daptomycin at doses of 5mg/kg every 48 hours. Mean concentrations of daptomycin in PD solution rapidly exceeded 1mg/l; again, these levels were higher than the MIC of daptomycin against most staphylococci.[2,3]

Huen SC et al[6] published the first cases of successful treatment with IP daptomycin in 2 patients with vancomycin-resistant *Enterococcus faecium* peritonitis. Doses of 200mg of daptomycin were administered diluted in PD solution (2l) followed by 20mg of daptomycin per litre of replacement fluid (every 4 hours) during 14 days. The purpose was to raise IP levels to more than 5 times higher than the MIC of daptomycin against enterococci (4mg/l). Once again, infection was resolved in these cases without adverse effects or complications arising from IP administration of the drug. These authors argue that its physical and chemical incompatibility with glucose appears not to compromise either its clinical efficacy or its antimicrobial potency, at least at low levels of glucose such as those in the PD solution in which this drug was diluted before administration.

Another case that deserves mention was published by Bahte SK et al[7] regarding a patient who had been on kidney replacement therapy with PD for 7 years and whose central catheter for total parenteral nutrition had to be removed on multiple occasions due to *Staphylococcus aureus* infections. The patient suffered an episode of sepsis related to the central catheter and was treated with IV daptomycin. After 5 weeks he was admitted with peritonitis judged to be a relapse of the prior septic process. Once the central catheter had been removed, doctors chose treatment with daptomycin for the peritoneal infection. Daptomycin dosed at 7mg/kg body weight (280mg total) was administered at the end of an Automated Peritoneal Dialysis (APD) session and the solution remained in the peritoneum for the next 12 hours. Blood samples were extracted at 0.5, 3.5 and 25 hours and a pharmacokinetic study of daptomycin was completed. Doctors observed that after IP administration of daptomycin, plasma drug levels rose above 10mg/l; once again exceeding the MIC of daptomycin against most bacterial strains. These authors call for more studies in order to determine whether or not IP administration of daptomycin might be useful in treating systemic infections in PD patients, especially those with difficult vascular accesses.

Two other cases of daptomycin treatment for peritonitis were recently published in this journal. The first case[8] describes a patient treated by our working group who received IP daptomycin. After 14 days of treatment the catheter was locked with 350mg of daptomycin in 7ml saline during 12 hours once weekly, coinciding with the PD dry day, for 1 month. In the second case,[9] the patient received IV daptomycin. Treatment was successful in both cases.

Peritonitis episodes in patients on PD often become recurrent infections because of biofilm formation. Biofilm formation is a complex process that begins when a bacterium adheres irreversibly to an abiotic surface, a tissue or a liquid-air interface. Once the bacteria adhere, they begin to divide and form a microcolony. The bacteria making up this microcolony begin to secrete substances such as polysaccharides and other macromolecules that form a three-dimensional structure. Micropores can be seen in this structure which bacteria use to exchange substances —both nutrients and waste products— with the medium. When the biofilm formation process is finished, some of the bacteria may leave this structure, adhere to another site on the surface and begin a new biofilm formation process.

When bacteria form part of a biofilm, their sensitivity to antimicrobial agents is different due to several reasons. The physical and chemical diffusion barrier formed by the exopolysaccharide matrix prevents antimicrobial agents from penetrating. In addition, growth of bacteria in the biofilm is slowed down due to nutrients being limited. There may be microenvironments that antagonise the antibiotic action. They activate stress responses that lead to changes in bacterial physiology and cause the appearance of a specific biofilm phenotype that actively combats the inhibitory effects of the antimicrobial substances.[10]

In light of the above, we must consider whether using MIC is the right strategy for evaluating antibiotic sensitivity in confirmed or suspected cases of biofilm-associated infections. A published study on this subject evaluated the sensitivity of 21 methicillin-sensitive strains of *Staphylococcus aureus* from PD patients with peritonitis using the MIC and the minimal biofilm eradication concentration (MBEC).[11] Antibiograms revealed that when MIC was used to determine bacterial sensitivity, all strains tested sensitive to all the antibiotics, but when the MBEC was used, all of the bacteria tested resistant or moderately sensitive to the same antibiotics. The only antibiotic to which strains were not resistant was the combination of vancomycin and rifampicin (1:1). Most of the strains were either sensitive or moderately sensitive to this treatment.

The disadvantage of using rifampicin in this type of patient is that it is physically and chemically incompatible with basic pH solutions. Most of the solutions used in PD are mildly basic liquids (pH = 7.4). In addition, this instability or incompatibility causes antimicrobial inefficiency, as demonstrated by Richards GK et al[12] in a study that showed that the pH of PD solutions was a determining factor in the response of *Staphylococcus epidermidis* biofilm to rifampicin. An acidic medium increased rifampicin's antimicrobial power, while basic and even neutral media (pH=7) inhibited its antibiotic activity.

Other antibiotics, such as linezolid, can be used in this type of infection due to their antibiotic spectrum, and in fact, there are several published cases of peritonitis[13,14] treated with linezolid, even orally, due to the drug's high bioavailability (100%). Recommendations for the treatment of PD-related peritonitis include the option of oral linezolid.[1] It can be administered by the IP route since its stability in PD solution has been tested.[15] However, it is also physically and chemically stable in solutions that are used less frequently at present (those with an acidic pH). So far, no cases of peritonitis treated with IP linezolid have been published in medical literature.

Another reason for discouraging use of linezolid in patients with recurrent peritonitis and suspected biofilm is that the drug is less active against biofilm. The *in vitro* study published by Raad I et al[16] showed daptomycin as the best option for eradicating methicillin-resistant *Staphylococcus aureus* (MRSA) embedded in biofilm three days after exposure to the antibiotic, compared to minocycline, tigecycline, linezolid, rifampicin and vancomycin. The difference was statistically significant ($P<.001$). Daptomycin's superior activity against biofilm was highlighted once again in the study by Smith K et al[17] in which the mean survival rate of MRSA cells in biofilm was 4% with daptomycin, compared to 62% with clindamycin, 45% with linezolid, 43% with tigecycline and 19% with vancomycin.

It is therefore interesting that, in light of currently available scientific evidence, daptomycin is a very effective option in the treatment of PD-related peritonitis in patients with suspected biofilm.

Within this panorama, daptomycin's true physical and chemical stability in PD solutions must be determined using validated laboratory tests. In addition, the drug's effectiveness in these patients must be assessed using randomised clinical trials comparing daptomycin with available alternatives in order to determine its placement within the treatment options for PD-related peritonitis.

Conflicts of interest

The authors affirm that they have no conflicts of interest related to the content of this article.

REFERENCES

1. Li PK, Szeto CC, Piraino B, Bernardini J, Figueiredo AE, Gupta A, et al. Peritoneal dialysis-related infections recommendations: 2010 Update. Perit Dial Int 2010;30:393-423.
2. Rybak MJ. The efficacy and safety of daptomycin: first in a new class of antibiotics for Gram-positive bacteria. Clin Microbiol Infect 2006;12 Suppl 1:24-32.
3. Burklein D, Heyn J, Kirchhoff C, Ozimek A, Traunmuller F, Joukhadar C, et al. Analysis of plasma and peritoneal fluid concentrations of daptomycin in a patient with Enterococcus faecium peritonitis. Int J Antimicrob Agents 2008;32(4):369-71.
4. Dvorchik B, Arbeit RD, Chung J, Liu S, Knebel W, Kastrissios H. Population pharmacokinetics of daptomycin. Antimicrob Agents Chemother 2004;48:2799-807.
5. Khadazhynov D, Joukhadar C, Peters H. Plasma and peritoneal dialysate levels during daptomycin therapy for peritonitis. Am J Kidney Dis 2009;53:911-2.
6. Huen SC, Hall I, Topal J, Mahnensmith RL, Brewster UC, Abu-Alfa AK. Successful use of intraperitoneal daptomycin in the treatment of vancomycin-resistant enterococcus peritonitis. Am J Kidney Dis 2009;54:538-41.
7. Bahte SK, Bertram A, Burkhardt O, Martens-Lobenhoffer J, Goedecke Vega, Bode-Böger S, et al. Therapeutic serum concentrations of daptomycin after intraperitoneal administration in a patient with peritoneal dialysis-associated peritonitis. J Antimicrob Chemother 2010;65(6):1312-4.
8. García-López L, Gómez Sayago L, Fernández-Reyes LMJ. Administración intraperitoneal de daptomicina. Nefrologia 2011;31(3):375-6.
9. Levy F, Camarero Termiño V, Blasco Moola A, Ortega Lafont MP, Abaigar Luquin P, Izquierdo Ortiz MJ, et al. Tratamiento con daptomicina intravenosa en una recidiva de peritonitis por Staphylococcus epidermidis. Nefrologia 2011;31(3):374-5.
10. Lasa J, Del Pozo JL, Penadés JR, Leiva J. Biofilms bacterianos e infección. An Sist Sanit Navar 2005;28(2):163-75.
11. Girard LP, Ceri H, Gibb AP, Olson M, Sepandj F. MIC versus MBEC to determine the Antibiotic Sensitivity of Staphylococcus aureus in Peritoneal Dialysis Peritonitis. Perit Dial Int 2010;30:652-6.
12. Richards GK, Gagnon RF, Obst G, Kostiner GB. The effect of peritoneal dialysis solutions on rifampin action against Staphylococcus epidermidis in the fluid and biofilm phases of growth. Perit Dial Int 1993;13(Suppl 2):341-44.
13. De Pestel DD, Peloquin CA, Carver PL. Peritoneal dialysis fluid concentration of linezolid in the treatment of vancomycin-resistant Enterococcus faecium peritonitis. Pharmacotherapy 2003;23: 1322-6.
14. Baley EM, Faber MD, Nafziger DA. Linezolid for treatment of Vancomycin-resistant enterococcal peritonitis. Am J kidney Dis 2001;38:1-3 (E20).
15. Manley HJ, Mc Claran ML, Bedenbaugh A, Peloquin CA. Linezolid stability in peritoneal dialysis solution. Perit Dial Int 2002;22(3):419-22.
16. Raad I, Hanna H, Jiang Y, Dvorak T, Reitzel R, Chaiban G, et al. Comparative activities of daptomycin, linezolid, and tigecycline against catheter-related meticillin-resistant Staphylococcus bacteremic isolates embedded in biofilm. Antimicrobl Agents Chemother 2007;51:1656-16.
17. Smith K, Perez A, Ramage G, Gemmell CG, Lang S. Comparison of biofilm-associated cell survival following in vitro exposure of meticillin-resistant Staphylococcus aureus biofilms to the antibiotics clindamycin, daptomycin, linezolid, tigecycline and vancomycin. Int J Antimicrob Agents 2009;33:374-8.

Sent to review: 11 Jul. 2011 | Accepted: 14 Nov. 2011