SHORT REPORTS

Gentamicin-Resistant Infections in Peritoneal Dialysis Patients Using Topical Gentamicin Exit-Site Prophylaxis: A Report of Two Cases

KEY WORDS: Gentamicin; prophylaxis; resistance.

Exit-site infections and peritonitis occurring because of periluminal entry of organisms along the peritoneal dialysis (PD) catheter tunnel are not infrequent and can be associated with adverse outcomes (1). The most studied antibacterial ointment is mupirocin, a topical agent with excellent activity against gram-positive organisms, which account for approximately 75% of exit-site infections (2). The application of mupirocin to the nares or the catheter exit site has been shown not only to reduce the risk of exit-site infection (3–6), but also peritonitis (4–6).

More recent studies have focused on gentamicin applied to the PD catheter exit site based on the hypothesis that topical gentamicin would be as effective as mupirocin for the prevention of gram-positive infections and more effective for the prevention of gram-negative infections, particularly those caused by *Pseudomonas*. In 2005, Bernardini *et al.* published the results of a randomized controlled trial comparing topical mupirocin with gentamicin for exit-site prophylaxis. Their study demonstrated that, compared with patients using mupirocin, those who used gentamicin cream for prophylaxis experienced fewer peritonitis episodes overall and a reduction in gram-negative peritonitis and exit-site infection (7). Two subsequent observational studies showed equivalent results with mupirocin and gentamicin (8,9).

Despite the favorable results with exit-site gentamicin, some practitioners have raised concerns about the potential for the development of gentamicin resistance, which would limit antibiotic options for the treatment of any subsequent gram-negative infections. To date, no gentamicin resistance has been reported.

Here, we report the cases of 2 patients using prophylactic topical gentamicin who developed exit-site infections with an organism that was found to be gentamicin-resistant.

CASE 1

A 73-year-old man with end-stage renal disease due to diabetes was started on automated PD in July 2007, with application of topical gentamicin ointment to the exit site with each dressing change. In October 2007, he was diagnosed with a coagulase-negative *Staphylococcus* exit-site infection for which he was treated with intraperitoneal vancomycin (because of resistance to cephalosporins and other oral agents). At that time, he was switched to mupirocin ointment with each exit-site dressing change. His pharmacy had no record of any new gentamicin ointment prescriptions after October 2007, but medication reviews from his routine clinic visits indicate that he used the remainder of his topical gentamicin for prophylaxis in September 2008 when he was delayed in refilling his mupirocin prescription.

The patient remained clinically well until October 2009, when he presented with purulent discharge and pain at the exit site. Culture of this discharge grew *Pseudomonas* species resistant to gentamicin. There was no evidence of associated tunnel infection, and effluent was clear. The patient was treated with oral ciprofloxacin for 2 weeks, with resolution of the exit-site infection. He had never received intraperitoneal or intravenous gentamicin.

CASE 2

A 70-year-old woman with a history of end-stage renal disease secondary to diabetic nephropathy was started on CAPD in December 2007, with application of mupirocin ointment to the exit site with each dressing change. She was transferred to a nursing home several months later, where mupirocin prophylaxis was continued by trained staff twice weekly. In October 2008, she developed a coagulase-negative *Staphylococcus* PD peritonitis, which resolved with a 2-week course of intraperitoneal vancomycin.

In November 2008, she was noted to have an erythematous and tender exit site, with growth of *P. aeruginosa* sensitive to gentamicin. She was treated with topical gentamicin daily for 7 days with good effect and was subsequently switched to gentamicin ointment for exit-site prophylaxis. The exit-site erythema returned

1 month later, and cultures again grew *P. aeruginosa*. A 14-day course of oral ciprofloxacin was prescribed, together with tobramycin intraperitoneally, and the infection resolved. A third *Pseudomonas* exit-site infection developed in March 2009 and was treated with oral ciprofloxacin and intraperitoneal tobramycin.

In discussion with the family and based on the patient's frailty, it was decided to treat with antibiotics and to avoid catheter removal and replacement. The exit site improved for a few weeks, but became inflamed again 1 month later, with growth of *P. aeruginosa* that was now resistant to gentamicin but sensitive to tobramycin. This patient had never previously received intraperitoneal or intravenous gentamicin.

DISCUSSION

Despite the benefit of applying prophylactic ointments for the prevention of exit-site infection and peritonitis, concerns have been raised about the potential for the development of bacterial resistance over time. Early data did not identify any mupirocin resistance after 1 year of exposure among PD patients (10), but mupirocin resistance has since been reported in several small studies, with a prevalence of 16% – 25% among carriers of *S. aureus* (11–13).

Since the publication of the randomized controlled trial by Bernardini *et al.* and the subsequent International Society of Peritoneal Dialysis recommendation that included gentamicin as an option for exit-site prophylaxis, many PD programs have adopted this regimen as part of their standard of care. Despite the increasing use of gentamicin over the past several years, there have been, before this publication, no reported cases of gentamicin resistance among PD patients using daily exit-site gentamicin. Based on the lack of reported gentamicin resistance to date, it is likely that such resistance is uncommon. However, the cases presented here suggest that such resistance may occur.

Interestingly, in the first of the two cases, gentamicin use had been interrupted before the gentamicin-resistant organism emerged, raising the possibility that intermittent use may facilitate development of resistance. In the second case, topical gentamicin was initiated as a treatment strategy and subsequently continued as prophylaxis against future *Pseudomonas* infections. It is unclear in that case whether gentamicin use in the presence of an established *Pseudomonas* infection facilitated the development of resistance.

The potential risk of resistance developing with chronic gentamicin exposure is supported by several studies in the hemodialysis literature, in which use of

prophylactic gentamicin catheter-locking solutions led to increased gentamicin resistance (14–16). In the largest of those studies, gentamicin use resulted in a significant reduction in catheter-related bacteremia, but infections with gentamicin-resistant organisms emerged within 6 months (14). Although those studies involved intraluminal instillation of gentamicin and not topical application, the findings suggest that chronic prophylactic exposure to aminoglycosides can breed resistance.

CONCLUSIONS

Our findings support the hypothesis that routine topical application of gentamicin may promote the development of resistant organisms in a subset of patients. It is possible that either intermittent use of gentamicin or use of gentamicin in the presence of an existing exit-site infection may increase the risk of resistance. Although the occurrence of gentamicin resistance in PD patients may be relatively uncommon, prospective tracking of the development of resistance is warranted to ensure that the frequency of gentamicin resistance is not underestimated.

DISCLOSURES

SJN has received speaker honoraria from Baxter Healthcare. SVJ has received speaker or consulting fees from Amgen Canada, Baxter Healthcare, and Ortho Biotec within the last 5 years.

Sharon J. Nessim^{1,2*}
Sarbjit Vanita Jassal³

Division of Nephrology¹
Jewish General Hospital
McGill University²
Montreal, Quebec, Canada
Division of Nephrology³
University Health Network
Toronto, Ontario, Canada

*email: sharon.nessim@mcgill.ca

REFERENCES

1. Davies SJ, Ogg CS, Cameron JS, Poston S, Noble WC. *Staphylococcus aureus* nasal carriage, exit-site infection and catheter loss in patients treated with continuous ambulatory peritoneal dialysis (CAPD). *Perit Dial Int* 1989; 9:61–4.
2. Mujais S. Microbiology and outcomes of peritonitis in North America. *Kidney Int Suppl* 2006; (103):S55–62.

3. Nasal mupirocin prevents *Staphylococcus aureus* exit-site infection during peritoneal dialysis. Mupirocin Study Group. *J Am Soc Nephrol* 1996; 7:2403–8.
4. Wong SS, Chu KH, Cheuk A, Tsang WK, Fung SK, Chan HW, *et al.* Prophylaxis against gram-positive organisms causing exit-site infection and peritonitis in continuous ambulatory peritoneal dialysis patients by applying mupirocin ointment at the catheter exit site. *Perit Dial Int* 2003; 23(Suppl 2):S153–8.
5. Thodis E, Bhaskaran S, Pasadakis P, Bargman JM, Vas SI, Oreopoulos DG. Decrease in *Staphylococcus aureus* exit-site infections and peritonitis in CAPD patients by local application of mupirocin ointment at the catheter exit site. *Perit Dial Int* 1998; 18:261–70.
6. Lim CT, Wong KS, Foo MW. The impact of topical mupirocin on peritoneal dialysis infection rates in Singapore General Hospital. *Nephrol Dial Transplant* 2005; 20:1702–6.
7. Bernardini J, Bender F, Florio T, Sloan J, Palmmontalbano L, Fried L, *et al.* Randomized, double-blind trial of antibiotic exit site cream for prevention of exit site infection in peritoneal dialysis patients. *J Am Soc Nephrol* 2005; 16:539–45.
8. Chu KH, Choy WY, Cheung CC, Fung KS, Tang HL, Lee W, *et al.* A prospective study of the efficacy of local application of gentamicin versus mupirocin in the prevention of peritoneal dialysis catheter-related infections. *Perit Dial Int* 2008; 28:505–8.
9. Mahaldar A, Weisz M, Kathuria P. Comparison of gentamicin and mupirocin in the prevention of exit-site infection and peritonitis in peritoneal dialysis. *Adv Perit Dial* 2009; 25:56–9.
10. Vas SI, Conly J, Bargman JM, Oreopoulos DG. Resistance to mupirocin: no indication of it to date while using mupirocin ointment for prevention of *Staphylococcus aureus* exit-site infections in peritoneal dialysis patients. *Perit Dial Int* 1999; 19:313–14.
11. Pérez-Fontán M, Rosales M, Rodríguez-Carmona A, Falcón TG, Valdés F. Mupirocin resistance after long-term use for *Staphylococcus aureus* colonization in patients undergoing chronic peritoneal dialysis. *Am J Kidney Dis* 2002; 39:337–41.
12. Lobbedez T, Gardam M, Dedier H, Burdzy D, Chu M, Izatt S, *et al.* Routine use of mupirocin at the peritoneal catheter exit site and mupirocin resistance: still low after 7 years. *Nephrol Dial Transplant* 2004; 19:3140–3.
13. Annigeri R, Conly J, Vas S, Dedier H, Prakashan KP, Bargman JM, *et al.* Emergence of mupirocin-resistant *Staphylococcus aureus* in chronic peritoneal dialysis patients using mupirocin prophylaxis to prevent exit-site infection. *Perit Dial Int* 2001; 21:554–9.
14. Landry DL, Braden GL, Gobeille SL, Haessler SD, Vaidya CK, Sweet SJ. Emergence of gentamicin-resistant bacteremia in hemodialysis patients receiving gentamicin lock catheter prophylaxis. *Clin J Am Soc Nephrol* 2010; 5:1799–804.
15. Venditto M, du Montcel ST, Robert J, Trystam D, Dighiero J, Hue D, *et al.* Effect of catheter-lock solutions on catheter-related infection and inflammatory syndrome in hemodialysis patients: heparin versus citrate 46% versus heparin/gentamicin. *Blood Purif* 2010; 29:268–73.
16. Abbas SA, Haloob IA, Taylor SL, Curry EM, King BB, Van der Merwe WM, *et al.* Effect of antimicrobial locks for tunneled hemodialysis catheters on bloodstream infection and bacterial resistance: a quality improvement report. *Am J Kidney Dis* 2009; 53:492–502.

doi:10.3747/pdi.2011.00224