Insufficient penetration of systemic vancomycin into the PermCath lumen

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Abstract

Background. Catheter infection is a major cause of morbidity and catheter loss in chronic haemodialysis patients. There has been a large discrepancy in the catheter salvage rate, after an episode of documented bacteraemia, whether the patients receive systemic antibiotic alone or systemic antibiotics concomitant with 'antibiotic-lock technique' (20–30% vs 100%, respectively). To test the hypothesis that vancomycin may not adequately penetrate into the lumen of the catheter, despite therapeutic plasma levels, a series of in-vivo, ex-vivo, and in-vitro experiments were performed.

Methods. We compared serum and intralumenal (0.3–0.5 ml aspirate from venous port of the catheter) vancomycin concentrations in 24 chronic haemodialysis patients, with documented bacteraemia, who had received prior systemic vancomycin therapy with 14 similar patients who had additionally received ‘vancomycin-lock technique’ (100 μg/ml of vancomycin in heparin solution) after each haemodialysis session.

Results. Despite serum vancomycin concentration of ~17 μg/ml in each group, the vancomycin concentration in the venous hub of the catheter was only 0.2 ± 0.6 μg/ml in the former group, in sharp contrast to 125.6 ± 13 μg/ml in the latter group. In the ex-vivo experiment, four uninfected PermCaths which had been removed were immediately fixed and studied with scanning electron microscopy. No cellular or fibrin barrier could be found at the terminal pore of the catheter interfering with the diffusion of vancomycin from plasma into the catheter lumen. In the in-vitro experiments, three PermCaths filled with standard heparin solution were incubated for 48 h in 100 ml of plasma containing 20 μg/ml of vancomycin. Vancomycin concentration was measured in 0.3–0.5 ml solution aspirated from each port of the catheters. Vancomycin concentration was 0.2 ± 0.1 μg/ml in the aspirated samples. Finally, two PermCaths filled with the standard heparin solution were incubated for 48 h in 100 ml of plasma containing 20 μg/ml of vancomycin, after which the catheters were sectioned at 4-cm intervals. Only the distal 4 cm of the catheters had vancomycin concentrations of 2 and 5 μg/ml, the remaining segments had levels ≤0.5 μg/ml.

Conclusion. Our results indicate that diffusion of vancomycin from plasma into the haemodialysis catheter is negligible. Thus, haemodialysis patients with central venous catheter who have to be treated for bacteraemia with systemic antibiotic therapy must always receive ‘antibiotic-lock technique’ of the catheter after each haemodialysis session.

Keywords: haemodialysis; vancomycin; sepsis; bacteraemia; PermCath

Introduction

Dual-lumen tunnelled, cuffed catheters are increasingly used for permanent vascular access in patients with limited access options for haemodialysis (HD). Infection of these catheters remains the leading cause of catheter loss, and constitutes a major source of morbidity and mortality in hospitalized patients. Since they are used three times a week for HD, bacteraemia from any source would potentially lead to bacterial seeding inside the lumen of these catheters. Whether bacteraemia is of catheter origin or is from other sources, e.g. urinary tract infection, cellulitis, pneumonia, etc., the treatment of bacteraemia should also aim at sterilization of the catheter.

The incidence of bacteraemia associated with chronic HD catheters is from 2 to 8 bacteraemic episodes per 1000 catheter days [1–3]. Gram-positive organisms are responsible for most of the catheter-related infections, with Staphylococcal infection accounting for 40–80%, and enterococci and Gram-positive bacilli accounting for the remainder of the infections [2,3,6–8]. The appropriate management of catheter-related bacteraemia, in patients undergoing HD, has not been clearly defined. Although clinicians agree about the need for intravenous antibiotics, they disagree about the need for catheter removal especially in haemodynamically stable patients and those who have had multiple
previous access failures with limited sites for future accesses. A 2–3 week course of appropriate systemic antibiotic therapy, without catheter removal, has resulted in catheter salvage in only 20–30% of these patients [3,4]. The role of antibiotic instillation into the catheter (‘antibiotic-lock technique’) to sterilize the catheter intraluminally has not been well defined. In the only one, uncontrolled study which evaluated the use of the ‘antibiotic-lock technique’ coupled with systemic antibiotic administration, 100% of the cases had successful eradication of bacteremia, with defervescence within 48 h and no complications [5]. Moreover, no patient required catheter removal, i.e. 100% catheter salvage rate. However, the study was not randomized or blinded, and did not have a placebo (‘heparin lock’) arm.

The discrepancy in the literature between 20–30% catheter salvage rate with systemic antibiotic alone versus 100% catheter salvage rate with systemic and ‘antibiotic-lock technique’ could be due to the fact that in the bacteraemic patients the use of the catheter for HD results in bacterial seeding inside the lumen of the catheter, and that systemic antibiotic therapy although achieving adequate serum antibiotic levels will not result in adequate antibiotic levels within the lumen of the catheter. To test this hypothesis we performed a series of in-vivo, ex-vivo, and in-vitro experiments to determine the degree of penetration of systemic vancomycin into the lumen of the PermCath.

Material and methods

In order to test the hypothesis that vancomycin may not adequately penetrate into the lumen of the catheter, despite therapeutic plasma levels, a series of four experiments (one in-vivo, one ex-vivo, two in-vitro experiments) were performed as follows. Throughout these experiments the catheters were filled with normal saline and heparin, at a final dilution of 1:1000 units. Vancomycin concentration was measured by AxSYM Vancomycin assay, based on fluorescence polarization immuno assay (FPIA) technology (Abbott AxSYM®, Abbott Laboratories, Abbott Park, IL).

In-vivo experiment

We studied 24 chronic HD patients who were receiving dialysis through a PermCath, and who had received intravenous vancomycin 48 h earlier, for an infectious complication. Vancomycin concentration was measured simultaneously in the plasma and in 0.3–0.5 ml solution aspirated from the venous port of the catheter, prior to HD session. The vancomycin levels were compared with another 14 chronic HD patients who had received systemic vancomycin and ‘vancomycin-lock technique’, i.e. 2 ml of heparin solution (1000 units/ml) containing 100 µg/ml of vancomycin had been installed in each port of the catheter 48 h earlier (the volume capacity of each port of PermCath is 1.6–1.8 ml). Systemic vancomycin therapy was generally administered after every second or third HD session (based on the pre-HD plasma vancomycin concentration), during the last 1–1.5 h of HD. The catheter was then rinsed with 300–400 ml of normal saline which is routinely infused into the patients at the end of HD to return the blood present in the dialyser.

Ex-vivo experiment

To rule out the possibility that a cellular or fibrin barrier, formed at the tip of the catheter occluding the pore, might have prevented vancomycin diffusion from plasma into the catheter lumen, four uninfected PermCaths which had been removed were immediately fixed in paraformaldehyde, and studied with scanning electron microscopy. The catheters had been removed because the patients had acquired a permanent vascular access.

In-vitro experiments

To test the possibility that there may be some hindrance to osmotic diffusion of vancomycin from plasma into the catheter lumen, three PermCaths filled with the standard heparin solution were incubated in 100 ml of plasma containing ~20 µg/ml of vancomycin. After 48 h of in-vitro incubation, vancomycin concentration in the plasma and in 0.3–0.5 ml solution aspirated from each port of the catheters were measured.

To determine the extent of penetration of vancomycin from plasma into the lumen of the catheter, two fresh PermCaths, filled with standard heparin solution, were incubated in 100 ml of plasma containing ~20 µg/ml of vancomycin. After 48 h of in-vitro incubation, catheters were sectioned at 4-cm intervals, starting from the tip of the catheter toward the hub. The solution inside each segment was tested for vancomycin concentration.

Statistical analysis

The data is expressed as mean ± SEM. Values were compared using Student’s t-test. Statistical significance was considered with P < 0.05.

Results

In-vivo experiment

In the 24 HD patients who had received systemic vancomycin alone, serum vancomycin concentration 48 h later was 17.0 ± 1.3 µg/ml. However, vancomycin concentration in the aspirate from the venous hubs of the catheters was only 0.2 ± 0.6 µg/ml. This was in sharp contrast to the 14 HD patients who had received similar systemic vancomycin therapy, as well as ‘vancomycin-lock technique’ in whom serum vancomycin concentration was 17.4 ± 1.5 µg/ml. However, vancomycin concentration in the aspirates from the venous hubs of the catheters was 125.6 ± 13 µg/ml.

Ex-vivo experiment

The scanning electron microscopy of four uninfected PermCaths that were removed 5–7 days after the last HD revealed no evidence of platelets, red blood cells or fibrin mesh causing a mechanical barrier at the terminal pore of the catheter. However, in two catheters there was an organized clot in the distal lumen
of the catheter. This experiment ruled out the possibility that a fibrin or cellular barrier, formed on the tip of the catheter, was responsible for the lack of diffusion of vancomycin from plasma into the lumen of the PermCath. However, the two catheters which had clots in their lumen could have had a mechanical barrier preventing the free diffusion of vancomycin in their lumen.

**In-vitro experiments**

After 48 h *in-vitro* incubation of three fresh PermCaths, filled with standard heparin solution, in 100 ml of plasma containing vancomycin (20 µg/ml), the plasma vancomycin concentration was measured $23 \pm 2.5\, \mu g/ml$ which was in sharp contrast to $0.2 \pm 0.1\, \mu g/ml$ obtained from the venous and arterial ports of each catheter (total of six samples, each 0.3–0.5 ml in volume). This experiment indicated that even in the absence of any cellular/fibrin component in the environment there was lack of adequate diffusion of vancomycin from plasma into the lumen of the catheter.

After 48 h *in-vitro* incubation of two fresh PermCaths in plasma containing vancomycin (20 µg/ml), only the most distal 4 cm of the catheters had vancomycin concentrations of 2 and 5 µg/ml. The remaining 4-cm segments had vancomycin concentrations $\leq 0.1\, \mu g/ml$. This suggested that vancomycin had only penetrated the most distal 4 cm of the catheter, despite 48 h of incubation in plasma containing adequate vancomycin concentration.

**Discussion**

Our *in-vivo, ex-vivo* and *in-vitro* experiments indicate that despite adequate vancomycin concentration in plasma, there is not adequate penetration of vancomycin into the lumen of the dual lumen cuffed HD catheters. Our results do not show any evidence of fibrin or cellular barrier in the pore located on the tip of the catheter preventing vancomycin diffusion into the catheter. The *in-vitro* studies further confirm that vancomycin simply does not diffuse to any significant degree from plasma into the heparin solution used to fill the catheter lumen, and that this lack of adequate diffusion is not secondary to a cellular/fibrin barrier. Finally, our experiments suggest that adequate vancomycin concentration is only achieved in the very distal 4-cm segment of the catheter, while the rest of the catheter lumen is not exposed to sufficient vancomycin concentration in the interdialytic period. Since HD catheters are used routinely three times a week for dialysis, which would lead to bacterial seeding inside the lumen of the catheter, lack of adequate vancomycin penetration into the lumen would result in inadequate antibiotic coverage for the bacteria which has already seeded the catheters intraluminally. Our *in-vivo, ex-vivo*, and *in-vitro* experiments suggest that the poor catheter salvage rate with systemic antibiotic therapy alone may be due to the lack of penetration of the antibiotic into the lumen of the catheter, and thus, persistence of bacteria intraluminally resulting in recurrence of infection after discontinuation of the antibiotic therapy. Thus, in HD patients with central venous catheters, who have to be treated for bacteraemia, systemic antibiotic therapy must always be associated with ‘antibiotic-lock technique’ of the catheter (after each HD session), since diffusion of the antibiotic from plasma into the catheter is negligible. Obviously, a prospective randomized double-blind placebo-controlled study is required to confirm the superiority of systemic antibiotic with concomitant ‘antibiotic-lock technique’ over systemic antibiotic therapy alone in this patient population.

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**References**


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