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Successful Use of Recombinant Tissue Plasminogen Activator in a Patient With Relapsing Peritonitis

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• **Intraperitoneal (IP) administration of either streptokinase (SK) or urokinase (UK) has assumed an adjunctive role to antibiotic therapy in selected patients with relapsing peritonitis. In these circumstances, bacteria may be protected from antibiotics through sequestration in either fibrinous structures or biofilms within the lumen of the peritoneal dialysis (PD) catheter or the peritoneal cavity. In some cases, it appears that disruption of these sheltered microenvironments by thrombolytic agents facilitated eradication of the offending organism and obviated the need for catheter removal, replacement, or interim hemodialysis. Although IP SK has been generally well tolerated as additive therapy in relapsing peritonitis, sporadic reports of significant complications, such as abdominal pain, fever, and severe hypotension, have precluded its more widespread acceptance. The only other thrombolytic agent used in this setting, UK, is presently unavailable because of a manufacturing shortfall. Therefore, adjunctive thrombolytic therapy for relapsing peritonitis is currently restricted. To circumvent these limitations, we devised an IP tissue plasminogen activator (tPA) protocol to eliminate recurring infection in a patient undergoing chronic ambulatory PD. After a third episode of peritonitis caused by *Enterobacter cloacae*, treated twice previously with an adequate antibiotic regimen, we instilled 6 mL of tPA (1 mg/mL) into the PD catheter for a 2-hour dwell time. The treatment was well tolerated and, in conjunction with a third course of antibiotic therapy, has produced an infection-free interval of 8 months.**

INDEX WORDS: Continuous ambulatory peritoneal dialysis (CAPD); peritonitis; tissue plasminogen activator (tPA).

PERITONITIS IS a serious complication for patients who undergo peritoneal dialysis (PD) as treatment of end-stage renal disease that frequently leads to hospitalization, catheter loss, and technique failure.[1] Afflicted patients usually present with abdominal pain and/or cloudy effluent. The white blood cell count in the effluent is usually 100/μL or greater, with at least 50% polymorphonuclear neutrophils.[1-5] Relapsing or recurrent peritonitis has been defined as a second episode of peritonitis caused by the identical organism that caused the immediately preceding infection and that arises within 2 to 4 weeks of discontinuing antibiotic therapy.[1,2] In addition to standard antimicrobial regimens, management of these cases involves a thorough search for a source(s) of relapsing infection and careful consideration of PD catheter removal (Table 1).[1-7]

Intraperitoneal (IP) thrombolytic drugs have been used successfully as a last pharmacological maneuver in some of these patients before resorting to PD catheter removal. To date, only streptokinase (SK) and urokinase (UK) have been used in this particular catheter salvage procedure. Presently, tissue plasminogen activator (tPA) is being used with increasing frequency in dialysis patients to declot thrombosed polytetrafluoroethylene grafts and restore and preserve the function of tunneled silastic elastomer hemodialysis catheters (A. Graham, personal communication, October 1999).[8,9] Although IP tPA administration has not been reported in humans, it has been safely used in several animal species.[10-18]

We were confronted with a therapeutic dilemma when a previously healthy patient undergoing continuous ambulatory PD presented with a third episode of relapsing peritonitis without a clear indication for catheter removal. In an attempt to eradicate infection and preserve his PD catheter, we used IP tPA as a therapeutic adjunct to directed antimicrobial therapy.

CASE REPORT

A 31-year-old black man undergoing continuous ambulatory PD presented with three episodes of peritonitis within 2 months. Selected relevant clinical information from each episode is listed in Table 2. The index infection manifested 2 days after the patient bathed in tap water without protecting

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Table 1. Indications for Early Catheter Withdrawal in Relapsing Peritonitis

Concurrent tunnel infection or certain exit-site infections
Coexisting intra-abdominal abscesses
Identification of certain pathogens (fungi, *Pseudomonas* species, *Xanthomonas* species, anaerobes, mycobacteria)
Failure to respond to initial therapy or clinical deterioration after therapy is initiated
Relapsing peritonitis of no apparent cause

NOTE. Recommendations from Piraino,[1] Keane et al,[2] and Tzamaloukas.[4]

the catheter. He rapidly responded to therapy at another institution with IP vancomycin and gentamicin and remained on this therapy for 2 weeks because of negative culture results. During a routine follow-up evaluation, he felt well, and abdominal examination was unremarkable. Analysis of the PD effluent showed a normal cell count and negative Gram stain results, but cultures of the effluent were positive for *Enterobacter cloacae*. Daily treatment with IP gentamicin was resumed for another 2 weeks, then discontinued. Two weeks later, he developed recurrent abdominal pain and cloudy effluent (Table 2). Again, rapid improvement and recovery were achieved with IP vancomycin and gentamicin. After the cultures showed positive results again for *E cloacae*, therapy was consolidated to oral ciprofloxacin, based on culture sensitivity data. One week after completing the course of ciprofloxacin, a third episode of peritonitis was detected. After empiric therapy with one dose of IP vancomycin and gentamicin, treatment was consolidated to oral ciprofloxacin and IP cefepime after growth of *E cloacae* was detected from the PD fluid.

At this time, the possibility of intermittent seeding of the peritoneal cavity from an intraluminal catheter reservoir of bacteria was considered. To avoid catheter removal, adjunctive therapy with an IP thrombolytic agent was considered. After reviewing existing protocols for the use of thrombolytic agents for dysfunctional hemodialysis and PD catheters and relapsing peritonitis, informal discussions were conducted with technical support representatives of Genentech, Inc (N San Francisco, CA), and a protocol was devised for IP administration of tPA in the form of recombinant alteplase (Activase; Genentech Inc).

Three weeks after therapy for the third episode of peritonitis had been initiated, the patient's abdomen was drained, and 6 mL of recombinant alteplase (1 mg/mL) was injected through the transfer set (priming volume, 1.8 mL) into the patient's PD catheter (Cruz, Wheeling, IL; priming volume, 6 mL) and allowed to dwell for 2 hours with the catheter clamped. The tPA was carefully aspirated, and a rapid exchange of 1 L of PD fluid was performed. Next, a 2-L exchange was performed immediately with 1 g of IP cefepime, which was allowed to dwell for 6 hours to optimize the exposure of bacteria to the antibiotic. No adverse reactions were observed within the immediate period of IP thrombolytic administration or over the next 3 days, during which time increased fibrin strands were detected in the PD fluid. Specifically, there was no abdominal pain, fever, or evidence of local or systemic bleeding. Three additional weeks of therapy with IP cefepime and oral ciprofloxacin were prescribed. Sampling of the effluent on the day of tPA administration and 3, 5, 10, and 25 weeks later showed normal results for cell analyses and negative culture results. The patient remained clinically asymptomatic throughout this period.

DISCUSSION

The index patient was an ideal candidate for catheter salvage by thrombolytic therapy because there was no suspicion of recurrent breaches of aseptic technique, no evidence of intra-abdominal pathological states that would predispose to recurrent peritonitis, and no apparent exit-site or tunnel infection. Other than the ex-

Table 2. Characteristics of Three Episodes of Peritonitis

	First Episode	Second Episode	Third Episode
PD effluent cell count, differential	Not available	779 WBC/μL, 91% neutrophils	1,500 WBC/μL, 75% neutrophils
PD fluid culture results	*Enterobacter cloacae*	*E cloacae*	*E cloacae*
Empiric therapy*	IP vancomycin, 2 doses; IP gentamicin, 2 wk	IP vancomycin, 1 dose; IP gentamicin, 1 wk	IP vancomycin, 1 dose; IP gentamicin, 1 dose
Refined therapy	IP gentamicin, additional 2 wk	Ciprofloxacin 500 mg PO BID, 1 wk	Ciprofloxacin 500 mg PO BID, 6 wk; Cefepime 1 g IP QD, 6 wk; 6 mL tPA (1 mg/mL) IP, one 2-h dwell†
Time to relapse‡	2 wk	1 wk	

Abbreviations: WBC, white blood cells; PO, orally; BID, twice daily; QD, daily.
*Adjunctive therapy with heparin, 1,000 U/L of PD fluid, was administered until effluent was clear.
†See text for details.
‡From the last dose of antibiotics.

pected minor degree of drug adsorption to the polyurethane catheter, we harbored no suspicion that tPA would react adversely with the catheter (T. Patapoff, personal communication, October 1999). Our patient had no relative or absolute contraindications to local or systemic thrombolytic treatment.

One prospective study and several case reports supported the use of either SK or UK as an effective component of therapeutic regimens of relapsing and/or resistant peritonitis.[19-28] Presumably, the thrombolytic agent enables the eradication of infection through physical perturbation of fibrin-coated microenvironments that shield the offending organism. These bacteria, previously sequestered from antibiotics, are thus rendered susceptible to their microbicidal actions.[19-22,26,27] Alternatively, some bacteria may be protected from antibiotics by their secretion of an exopolysaccharide layer of biofilm, which has been shown on the inner aspect of peritoneal catheters by electron microscopy.[29] In some instances, this biofilm was postulated to be the source of relapsing infection and was also believed to contribute to antibiotic resistance.[29–33] Although thrombolytic agents do not affect the growth of biofilm, they may induce qualitative structural alterations of the exopolysaccharide architecture that facilitate antibiotic penetration.[26] Thus, in appropriate circumstances, IP instillation of thrombolytics may spare patients the discomfort and expense of repeated catheter implantation.[19,22,26,27]

Significant variability exists among published protocols regarding thrombolytic therapy in patients with end-stage renal disease who undergo either PD or hemodialysis. The indications for treatment (eg, clotted hemodialysis catheter, obstructed PD catheter, and relapsing peritonitis), type and dose of thrombolytic administered, infusate volume, and dosing interval vary widely. For example, Pickering et al[22] recommend instilling 7,500 IU of UK, diluted in 5 mL of saline, into the PD catheter for a 2-hour dwell time for selected individuals with relapsing peritonitis. Others have injected 75,000 IU of UK into a 2-L bag of dialysate and instilled the contents for 30 to 60 minutes into patients with relapsing peritonitis or, alternatively, injected the same amount of UK mixed in 40 mL of diluent directly into the PD catheter for an equivalent period to treat outflow obstruction.[24] Another group reported success with a much lower dose of 5,000 IU of UK in obstructed PD catheters.[25] The National Kidney Foundation–Dialysis Outcomes Quality Initiative guidelines for obstructed hemodialysis catheters recommend that UK, 5,000 U/mL, be instilled into each catheter lumen for a dwell time of 30 minutes.[34] In the protocol of Paulsen et al,[8] clotted hemodialysis catheters are injected with tPA at a concentration of 1 mg/mL in sufficient volumes to fill each catheter lumen and left for varying periods of 30 minutes to 4 days before removal. The regimen designed and implemented in our patient represents an amalgam of these published protocols.

Adverse effects related to the IP administration of SK or UK have been infrequent and mostly ascribed to SK. Importantly, there have been no reports of systemic bleeding complications related to IP delivery of these drugs, including cases in which IP SK was used to restore function of clotted PD catheters in patients who developed active abdominal wall bleeding after insertion of their PD catheters.[35-37] The notation that conventional laboratory parameters of hemostasis remain unaltered after IP SK and UK administration suggests that these drugs are not significantly absorbed across the peritoneal membrane.[36,38] For this reason, some investigators no longer routinely measure hemostasis parameters during IP thrombolytic use.[24] Recombinant alteplase (molecular weight [MW], 65,000 d) is larger than either UK (MW, 54,000 or 34,000 d) or SK (MW, 47,000 d) and has a biological half-life shorter than both, which implies its favorable comparison to UK and SK regarding the risk for inducing systemic hemorrhage during IP delivery.

IP tPA has been administered to animals to reduce the development of postoperative adhesions and abscesses in models of peritonitis and intra-abdominal injury. In all but one of the investigations that we reviewed, IP tPA at doses similar to or greater than that used in our patient did not cause significant hemorrhagic complications in the rabbit,[10-14] rat,[15-17] or dog.[18] In one study, 10 mg of IP tPA caused fatal intra-abdominal hemorrhage after surgically induced uterine trauma in several rabbits.[39] Because IP tPA administration has not been studied in hu-

mans, we recommend applying standard exclusion criteria used for systemic delivery of thrombolytic drugs to candidates for whom IP tPA is being considered until further information becomes available.

The index patient sustained a 3-week delay between the initiation of antibiotic therapy for his third episode of peritonitis and treatment with tPA because of the unavailability of UK and the unwillingness of the patient to be administered SK. Ideally, IP tPA should be implemented within a few days of the diagnosis of relapsing peritonitis, and antibiotics should be continued for an additional 2 to 4 weeks. We augmented the provision of tPA with a daily dose of IP cefepime in the hope that continuous incubation of the catheter lumen in an antibiotic would synergize with the disruption of a presumptive catheter biofilm. Single daily dosing was preferred in favor of a continual dosing schedule because of patient-specific factors. Although ciprofloxacin therapy may have been redundant in this case, it was continued because of uncertainty regarding the merits of daily versus continuous IP cephalosporin treatment of gram-negative bacillary relapsing infection.

In conclusion, the combination of IP tPA and antibiotics was used to successfully treat a patient with relapsing peritonitis caused by *E cloacae*. We speculate that IP thrombolytic therapy facilitated eradication of the infection and preserved this patient's peritoneal catheter. However, this point cannot be definitively concluded because of the differences in choice, duration, and modality of antibiotic administration in the last peritonitis episode. Because of our success in this case, we contend that use of adjunctive IP tPA in carefully selected cases of relapsing peritonitis and/or obstructed PD catheters warrants further investigation. Furthermore, we believe that a randomized multicenter trial that directly compares IP tPA with placebo or another thrombolytic agent(s) should be undertaken to clearly define the safety and efficacy of IP tPA. Pretreatment and posttreatment parameters of hemostasis should also be incorporated into such trials.

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