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Bulletin de la Dialyse à Domicile

# Peritoneal dialysis catheter dysfunction due to fibrin clots following treatment with tranexamic acid: a clinical case

(Dysfonction du cathéter de dialyse péritonéale due à des caillots de fibrine suite à un traitement par acide tranexamique : un cas clinique)

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**Résumé**

Les patients insuffisants rénaux chroniques (IRC) présentent un risque plus élevé de thrombose artérielle et veineuse, mais également de complications hémorragiques. L'acide tranexamique est une molécule anti-fibrinolytique qui inhibe le clivage de plasminogène en plasmine et est utilisé dans les syndromes hémorragiques (polytraumatisé, hémorragies gynécologiques ou digestives).
Nous rapportons un cas original d'utilisation de l'acide tranexamique (Exacyl®) chez une patiente en dialyse péritonéale qui présentait une hémorragie digestive inexpliquée. Le traitement par acide tranexamique a été compliqué par une dysfonction du cathéter de Tenckhoff en raison de son obstruction par des caillots de fibrine dans le dialysat.
La cinétique de survenue des caillots de fibrine juste après la mise en route du traitement chez une patiente n'ayant jamais présenté ce type de complications ni avant le traitement, ni après son arrêt ainsi que son pouvoir anti fibrinolytique sont en faveur d'une implication de ce traitement.

Mots clés : dialyse péritonéale, acide tranexamique, fibrine, hémorragie digestive

**Summary**

Chronic kidney disease patients experience not only more frequent arterial and venous thrombosis but also hemorrhagic episodes. Tranexamic acid is an anti-fibrinolytic molecule that inhibits plasmin activation. It is used in hemorrhage cases (post-traumatic, gynecologic, or gastrointestinal bleeding).
We report on an original case of tranexamic acid (Exacyl®) use in a peritoneal dialysis patient for gastrointestinal bleeding of unknown origin. The use of tranexamic acid led to the Tenckhoff catheter dysfunction because of fibrin clots in the dialysate.
The emergence of fibrin clots a few days after the start of tranexamic acid treatment, which never occurred again after the end of the treatment, and the anti-fibrinolytic function of tranexamic acid favors this treatment's role in fibrin clot occurrence.
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Key words : peritoneal dialysis, tranexamic acid, fibrin, digestive hemorrhage

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## INTRODUCTION

Patients with chronic kidney disease (CKD) are at increased risk for arterial and venous thrombosis [1–6]. Numerous mechanisms lead to an increased risk of thrombosis, and the frequency of arterial thrombosis is not explained solely by traditional cardiovascular risk factors (smoking, obesity, dyslipidemia). The role of uremic toxins has been proposed [7,8]. In addition to thrombotic risk, CKD patients also have a higher risk of hemorrhagic accidents, particularly digestive hemorrhages, intracranial bleeding, and, more commonly for hemodialysis patients, bleeding at arteriovenous fistula puncture points. A history of bleeding is found in 40% to 50% of CKD patients [9]. Therefore, the therapeutic management of CKD patients sometimes consists of a subtle balance between antithrombotic treatment and therapeutic abstention.

In hemodialysis, hemorrhagic accidents force sessions without anticoagulants, which often lead to the loss of hemodialysis circuits and worsen the anemia of patients, but in peritoneal dialysis (PD), the use of anticoagulants is not necessary. This is one of the many advantages of the technique.

Tranexamic acid (TA) is a synthetic derivative of lysine that inhibits the cleavage of plasminogen to plasmin, which is a fibrinolytic enzyme in the coagulation system; that is, it dissolves fibrin from the blood clot. TA is therefore an anti-fibrinolytic. This treatment is used in France for the following indications: hemorrhagic accidents after fibrinolysis, menorrhagia and metrorrhagia, digestive hemorrhages or hematuria of low origin, and otorhinolaryngological hemorrhages (adenoidectomies and tonsillectomies) [Source: Haute Autorité de Santé].

The adverse effects of TA are on the one hand allergic reactions to the product and on the other hand thrombotic events [10]. TA should be used with caution in CKD patients, as it is 90% excreted in the urine, and there is a risk of accumulation and occurrence of thrombotic events in these patients [11]. Seizures have also been reported with accumulation [12,13]. We report an original case of TA used in a PD patient who presented with unexplained lower gastrointestinal bleeding that led to Tenckhoff catheter dysfunction by obstruction as a result of fibrin clots in the dialysate.

## CLINICAL CASE

The patient, a 67 years-old woman, has been receiving PD since October 2018 for chronic tubulointerstitial nephritis.

Her past medical history was : long-standing hypothyroidism, a traffic accident at age 35 with left foot surgery complicated by deep venous thrombosis and pulmonary embolism, rheumatoid arthritis under corticosteroids, and smoking cessation.

The patient was autonomous in automated PD (APD). She dialyzed 6 days a week, 8 hours per night, with 4 exchanges of 2000 mL of glucose dialysate (Physioneal® 40 1.36%, Baxter) and 2000 mL of icodextrin (Extraneal®, Baxter) during the day with a Tenckhoff swan-neck catheter. Her latest results were a Kt/V of 1.7, a creatinine clearance equal to 50 L/wk/1.73m$^2$, and a highly permeable peritoneum on her last peritoneal equilibration test.

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In October 2019, while the patient was on the national renal transplant waiting list, she presented with acute anemia at 4 g/dL without externalization, requiring the transfusion of four red blood cell packs. Iron and vitamin deficiency was demonstrated, supplemented by an infusion of 500 mg of ferric carboxymaltose (Ferinject®, Vifor Pharma), folic acid (Speciafoldine®), and erythropoietin (Mircera®, Roche, 200 $\mu$g per month). She underwent esogastroduodenal fibroscopy, finding unulcerated erythematous antritis as well as a highly inflammatory mucosa without the presence of Helicobacter pylori, for which the proton pump inhibitors were increased by 40 mg in the morning and evening.

In November 2019, the patient presented with asthenia and worsening dyspnea. A checkup found anemia at 5g/dL, for which the patient was again transfused with two red blood cell packs. The patient had described dark stools for a week. A colonoscopy was performed, which had normal results.

A video capsule was requested but would not take place until August 2020 because of the health context and the patient's reluctance to undergo the examination. This showed intense erosive gastritis but no lesion of the small intestine.

In November 2020, the persistence of slow deglobulization led to an increase in erythropoietin (from Mircera® 200 $\mu$g per month to Aranesp®, Amgen, 300 $\mu$g/week). The patient also underwent an upper enteroscopy in the hypothesis of angiodysplasia of the small intestine following the opinion of the gastroenterologist. This examination did not reveal any lesion explaining the bleeding.

With the absence of visible lesion on endoscopies or on the videocapsule and the melena episode as well as the persistence of episodes of deglobulization leading to suspicion of angiodysplasias not seen on endoscopies, it was decided to put the patient on TA (Exacyl®, Cheplapharm) 500 mg: 1 tab/day on December 18, 2020.

On January 15, 2021, the patient reported drainage problems overnight with her cycler. She had to stop dialysis in the middle of the night.

The patient was admitted to the PD unit. She received an unprepared abdominal X-ray that showed the Tenckhoff catheter was in place. A 2000 mL continuous ambulatory PD exchange (CAPD) performed by PD nurses proceeded without issues, with rapid drainage, rapid infusion, and clear liquid. The patient returned home, and the following dialyses went well.

On January 26, 2021, the patient recontacted the PD center for the same drainage problems with a cycler that repeatedly alarmed "Check patient line" (Figure 1). The patient was admitted to the PD unit again, this time bringing her overnight drainage bag. Several pieces of fibrin were evident in the night PD bag although the patient had never had fibrin in the bags (Figure 2). The involvement of TA treatment was suspected in the formation of fibrin in the dialysate. This treatment was stopped, but no other treatment was started, particularly no heparin in the dialysate bags. The fibrinogen level on January 19, 2021, was 7.3 g/L.

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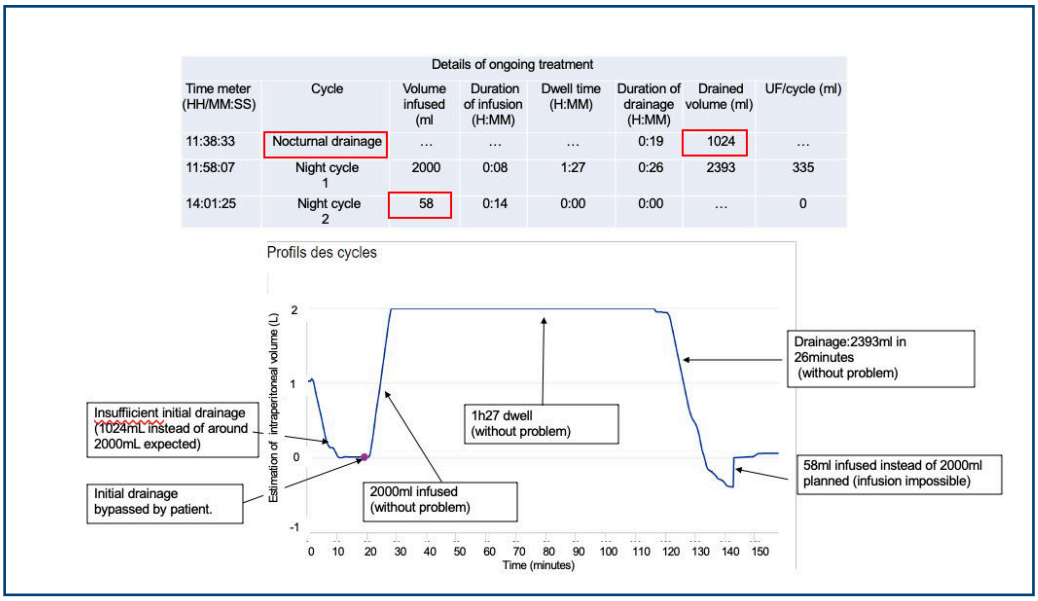
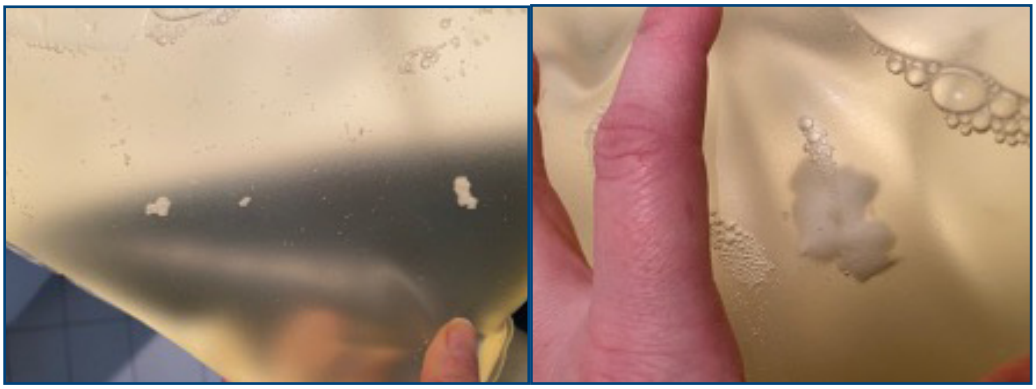



⬆ *Figure 1. Peritoneal dialysis session on January 26, 2021: session data and drainage curve*

*We can see here that the initial drainage was difficult, with an insufficient drainage alarm after 1024 mL while the patient had infused 2000 mL on the previous-day cycle. The patient manually bypassed the drainage (that is, she stopped the drainage and moved on to the next cycle's infusion). The following infusion and drainage went smoothly, but the second injection was not possible. Only 53 mL of the planned 2000 mL was infused. The catheter was completely blocked, and "Check patient line" alarms followed. The patient was forced to stop treatment.*



⬆ *Figure 2. Fibrin fragments visible inside the peritoneal dialysis bag*

Two days later, the patient returned with the same problem. The catheter was completely blocked, and it was impossible to drain or infuse dialysate despite repeated rinses of the catheter with the syringe with physiological saline. The patient benefited from a lock of the urokinase + taurolidine catheter with the following protocol: TauroLock® U (Theradial) 50000 IU diluted in 5 mL of the solvent supplied with the product, and 4.5 mL (volume of the Tenckhoff swan-neck catheter + extension line) was injected slowly into the patient's catheter. Once this operation was complete, a betadine plug was put back on the catheter and was allowed to act between three and four hours, and then the dialysate was drained. This lock failed to regain catheter patency. The heparin catheter (concentration of 2500 IU/ml) was locked according to the same protocol as above, allowing for the excellent functionality of the catheter to be restored. The dialysate bags were then heparinized with 2500 IU of heparin in each 2 L bag for 24 hours. Since this episode,

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the patient has resumed APD according to her previous protocol; no new episode of dysfunction or any fragment of fibrin has appeared after a three-month follow-up. Her hemoglobin level was stable and normal, and her last fibrinogen from March 23 was 6.5 g/L. TA has been permanently stopped (Figure 3).

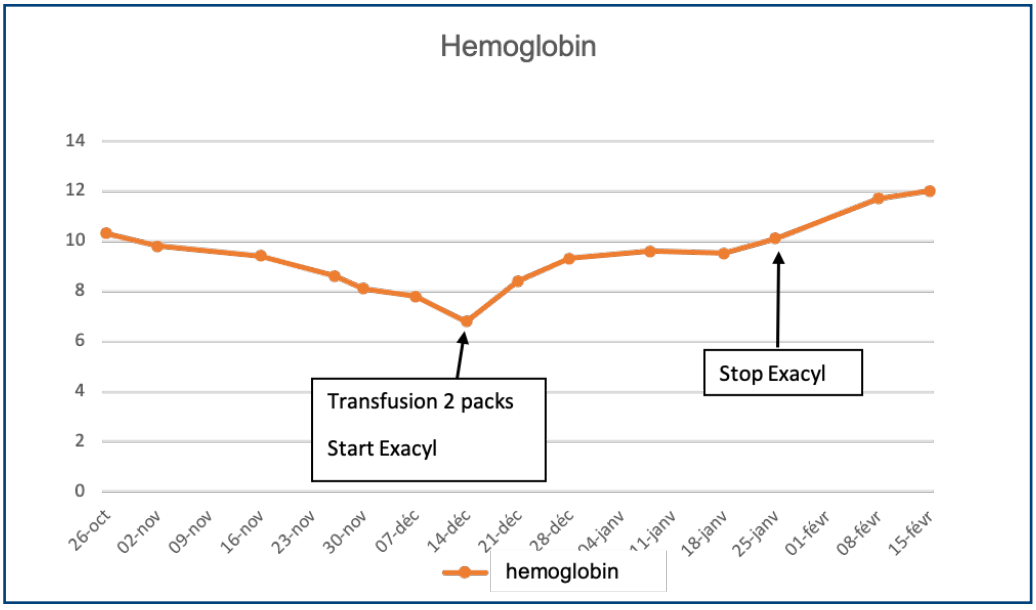


*Figure 3. Evolution of the patient's hemoglobin level*

## DISCUSSION

We reported an original case of Tenckhoff catheter obstruction by fibrin during treatment with TA (Exacyl®) in a PD patient responsible for the inability to continue PD. In the reported case, stopping the TA and anticoagulant and fibrinolytic locks associated with continuous ambulatory PD peritoneal flushes repermeabilized the Tenckhoff catheter, cleared fibrin clots, and resumed APD. However, this situation almost necessitated a surgical desobstruction of the catheter. To our knowledge, this is the first case of this type reported in the literature.

We cannot definitively say that TA was responsible for the appearance of fibrin clots, but this patient had never presented fibrin clots in the dialysate before and has not shown any since with a decline of several months. The anti-fibrinolytic role of TA and the kinetics of clots therefore make the triggering role of treatment very likely in the onset of this complication.

Using the French drug imputability method, the intrinsic imputability score was classified as likely [I3] on a scale from I0 (incompatible imputability) to I4 (very likely imputability). In fact, concerning the chronological criterion, the time to onset was compatible and the evolution suggestive, which made the drug's imputability plausible (classified C2). Regarding the semiological criterion, the semiology was suggestive of the role of the drug, there was no specific imputability test, and we did not find a nondrug cause, which made the drug's imputability plausible (S3).

In the literature, TA is suggested in hemorrhagic syndrome. The early treatment of polytrauma patients has shown a benefit to their survival at four weeks in a randomized study called

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CRASH-2, which included more than 20,000 patients [14,15]. In this study, the earlier the treatment was administered (<3h), the more beneficial it was.

After cardiac surgery, the administration of TA reduced the need for transfusion and improved survival in a 2012 meta-analysis of more than 10,400 patients in 127 studies [16]. TA has also been suggested in postpartum hemorrhages. In this indication, there appears to be a beneficial effect on the number of transfusions, but the number and size of studies in this area are low, and more studies are needed [14].

In gastrointestinal bleeding, the level of evidence is lower. A recently published randomized study analyzed the benefit of TA on the survival of patients with gastrointestinal bleeding. This study, which included just under 12,000 patients, was negative and found an increase in deep-vein thrombosis (0.8% with AT vs 0.4% with placebo, RR 1.85; 95% CI 1.15 to 2.98) 17. One of the major biases of this research is that the primary focus was changed during the study, as patients who died did not have bleeding, and bleeding mortality was substituted by all-cause mortality.

The use of TA in PD patients has been poorly reported in the literature. An experimental study conducted in rats in PD showed a benefit of TA to ultrafiltration [18]. In a small human study (n = 15) from 2009, TA also improved ultrafiltration in DP [19] patients. In this study, TA also improved urea and creatinine clearances.

To our knowledge, no other study has reproduced this result in humans. No other study in the literature has reported the appearance of fibrin clots in the dialysate after the use of TA in patients with PD. To our knowledge, no case of venous thrombosis has also been reported in PD patients receiving this treatment.

In conclusion, we reported an original case of Tenckhoff catheter dysfunction by obstruction of fibrin clots after TA administration. TA should be used with caution in this population, as this treatment may jeopardize the correct functioning of the technique.

## Disclosure

*The authors declare no conflict of interest for this article.*

## Contribution of authors

*Elodie Bogner, Elodie Ferrero and Joëlle Marin were the nurses in charge of the patient. They helped to collect data and write the paper.*

*Stanislas Bataille was the nephrologist of the patient. He wrote the paper and obtained consent from the patient to participate to the study.*

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