Case Report

Tranexamic Acid Treatment of Life-Threatening Hematuria in Polycystic Kidney Disease

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A 41-year-old woman with autosomal dominant polycystic kidney disease had chronic kidney disease class IV. She presented 10 days postpartum with a 4-day history of severe hematuria, left flank pain, and anemia, hemoglobin 62 g/L. CT scan showed massively enlarged kidneys with multiple cysts; several cysts bilaterally had high attenuation consistent with hemorrhage. Hematuria persisted over several days despite intensive conservative measures that included vitamin K1, 4 units of plasma, transfusion of 10 units of packed RBCs, Darbopoeitin, and DDAVP. Antifibrinolytic therapy was given with tranexamic acid 1000 mg p.o. t.i.d for one day then OD. The hematuria stopped within 24 hours and did not recur after tranexamic acid therapy ended. Over the next 4 years there were 3 hospitalizations each with severe gross hematuria requiring blood transfusion for acute anemia. The hematuria responded well to further treatment with tranexamic acid. Tranexamic acid produces antifibrinolytic effects via complex interactions with plasminogen, displacing plasminogen from the fibrin surface. Chronic renal impairment is considered a relative contraindication to use of tranexamic acid due to reports of ureteric clots and acute renal failure from cortical necrosis. We conclude that tranexamic acid can be used safely in some patients with CKD and polycystic kidney disease to treat severe hematuria.

1. Background

Hematuria is a common problem in patients with polycystic kidney disease (PCKD), with 42% of patients experiencing at least one episode of gross hematuria [1]. This is usually controlled with medical therapy and rarely needs surgical intervention. Although self-limited, cumulative episodes of gross hematuria may have an unfavorable impact on long-term renal function [1].

Here we describe a case of recurrent severe hematuria in PCKD treated successfully on six occasions with tranexamic acid (TA), an antifibrinolytic agent that competitively inhibits the activation of plasminogen to plasmin [2].

2. The Case

A 41-year-old Caucasian woman was diagnosed at age 12 with autosomal dominant PCKD. She presented to the emergency room 10 days after normal spontaneous vaginal delivery with a four-day history of gross hematuria and left flank pain. She was taking hydromorphone for flank pain and labetalol for hypertension. On physical exam she was pale with hypoxemic O2 saturation 96% on 3 L nasal cannula, and she had fever (38.7) with normal BP and pulse rate (BP 136/90 mmHg. PR94bpm). She had high JVP (6 cm above the sternal angle), normal heart sounds, bilateral basal crackles on chest examination and markedly enlarged irregular nontender kidneys.

Urinalysis showed large blood and 3–5 WBCs/hpf with no proteinuria. Hemoglobin was 62 g/L from a baseline of 132 g/L several months prior. Her electrolytes were normal. Urea was 16.8 mmol/L and creatinine 315 μmol/L, eGFR (MDRD) 15 mL/min/1.73 m^2. INR was 1.9, PTT, and platelets were normal. Chest X-ray revealed pulmonary edema.

Echocardiogram showed dilated cardiomyopathy with ejection fraction of 18%. Unenhanced CT scan showed massively enlarged kidneys with multiple cysts; there were several cysts bilaterally with high attenuation consistent with

hemorrhage but no stones, masses, or tumours. MRI showed a large hemorrhagic cyst within the left kidney but otherwise the same findings as the CT scan. Patient underwent cystoscopy, and blood was seen coming from the left ureteric orifice, with no evidence of obstruction. Renal angiogram failed to reveal a major bleeding site.

The patient was treated for possible sepsis and urinary tract infection with intravenous antibiotics: Cefazolin 1 gm every 12 hours, Clindamycin 600 mg every 8 hours, and Ciprofloxacin 400 mg daily. Blood and urine cultures were negative, and antibiotics were stopped on the 2nd day of admission.

The hematuria was managed conservatively with vitamin K 10 mg subcutaneously daily for 5 days, Darbepoietin 80 mcg subcutaneously once weekly, plus 4 units of plasma to correct the coagulopathy. DDAVP 20 mcg intravenously daily was given for 6 days. However gross hematuria continued, despite daily transfusions of pRBCs total of 10 units. Hemoglobin remained around 70 g/L. Consideration was given to a left nephrectomy.

3. Management

Because of high surgical risk with poor cardiac status and the long-term impact of nephrectomy on kidney function, antifibrinolytic therapy was given with TA (Cyklokapron, Pfizer Canada Inc., QC) 11 mg/kg (1000 mg) orally three times a day for one day then once daily for 5 days.

The hematuria stopped within 24 hours and did not recur after TA therapy was stopped. Hemoglobin stabilized at 95 g/L. Kidney function improved; serum creatinine fell to 224 μmol/L on discharge.

She presented five days after discharge with dyspnea and bilateral lower limb edema and was thought to have a deep venous thrombosis. She was given Dalteparin 200 units/kg subcutaneously. Doppler ultrasound of the leg veins was normal but she again developed hematuria which persisted despite stopping the Dalteparin. She was treated with TA 11 mg/kg orally twice a day for one day then once daily for 5 days. The hematuria stopped within 24 hours and did not recur after TA therapy ended. Serum creatinine was stable during this admission.

The patient presented 2 years later with a ten-day history of gross hematuria and left-sided flank pain. She had been given Co-trimoxazole one DS tablet twice a day for five days for presumed urinary tract infection. Hemoglobin was 77 g/L, and serum creatinine was 560 μmol/L compared with 120 g/L and 360 μmol/L, respectively, a month before. Coagulation profile was normal, urine grew normal flora, and Co-trimoxazole was stopped. She was treated conservatively and received total of 4 units of packed red blood cells, and DDAVP 20 mcg intravenously daily for 3 doses. The hematuria continued. TA 15 mg/kg was given 3 times a day for 3 doses then daily for 3 doses. Hematuria stopped within 24 hours. She developed mild nausea that responded to Metoclopramide. Hemoglobin stabilized at 100 g/L, and serum creatinine fell to baseline.

Six months later she presented with one-week history of gross hematuria. Despite Darbepoetin therapy, hemoglobin had fallen from 111 g/L a month before to 76 g/L. Serum creatinine rose from 400 μmol/L a month prior to 450 μmol/L. She had no flank pain, fever, or urinary symptoms. She was transfused with 2 units packed red blood cells and given TA 10 mg/kg intravenously daily for 3 doses. The hematuria stopped within a day, and she was discharged with hemoglobin 91 g/L and renal function went back to baseline.

Twelve and sixteen months after her last admission, she presented with painless hematuria and was treated as an out patient with TA 11 mg/kg orally daily, and her hematuria resolved within 24–36 hours after the first dose on both occasions.

The patient progressed to end-stage renal disease and was started on hemodialysis four years after the initial presentation.

4. Discussion

Gross hematuria is a common manifestation of PCKD. It can result from trauma, renal calculi, tumor, or infection. Spontaneous cyst bleeding is important to consider in this particular group of patients; it can be prolonged by local activation of fibrinolysis by urokinase [3].

The management of hematuria in PCKD is usually conservative with bed rest, blood transfusion, correction of coagulopathies, use of DDAVP, and erythropoietin stimulating protein. Nonetheless, other modalities have been tried to avoid prolonged hospitalization and nephrectomy and to preserve kidney function. These include other antifibrinolytic agents such as aprotinin and epsilon aminocaproic acid (EACA) [3].

We report rapid cessation of hematuria in PCKD on four occasions with administration of TA, a potent fibrinolysis inhibitor. TA or trans-4-(aminomethyl) cyclohexanecarboxylic acid is approximately 10 times more potent in binding to plasminogen than EACA and is better tolerated [4]. It is a synthetic amino acid which reversibly blocks the lysine binding sites on plasminogen; these are important for binding to fibrin and subsequent activation by plasminogen activators and fibrinolysis [5]. In the setting of renal impairment TA improves platelet function and shortens bleeding time [6]. It has also proved to be beneficial as adjunctive therapy in major upper GI bleeding including that occurring in dialysis patients [7].

Successful TA therapy of life-threatening hematuria in PCKD has been reported previously in a single patient [8]. TA was given at a dose of 20 mg/kg IV followed by 20 mg/kg orally every 2 days for 2 months.

In our case TA stopped bleeding within 24–36 hours on each of four occasions. There were no significant side effects apart from mild nausea with the third treatment. The nausea on this occasion may be due to the use of TA at a higher dose on the first day. In addition it could have been due to reduced renal function with transient uremia. In all four episodes kidney function either stabilized or improved after TA therapy. This is probably due to correction of a prerenal element since TA has no direct effect on kidney function in patients with chronic renal impairment [6].

Renal hematuria is considered a contraindication for TA treatment, because it may cause bladder and ureteral occlusion by clots. This complication can be successfully resolved with a double J stent [8]. In addition there are reports of acute renal cortical necrosis after use of TA. In one case, a 37-year-old man with baseline serum creatinine of 80 μmol/L received high dose TA to treat hemoptysis (3 gm IV daily for five days). Serum creatinine was 610 μmol/L on the 6th day [9]. In another case a 21-year-old man with hemophilia A who received TA for epistaxis at the same high dose (3 gm iv daily for 4 days), 3 days later his creatinine was 336 μmol/L and after 6 days serum creatinine has risen to 716 μmol/L [10]. We believe that this complication may be due to the use of high dose TA over several days. Another possible side effect of TA is increased risk of thrombosis. However, In a recent review, Tengborn questions the association of TA use and thrombosis given the lack of excess cases in TA studies involving cardiac surgery, total knee and hip arthroplasty, bleeding disorders of pregnancy, and menorrhagia [11]. This risk is sometimes thought to be higher in hemophiliac patients with hematuria. However in our case the patient had no known history of bleeding disorder.

TA accumulates in the presence of reduced kidney function as it is excreted by glomerular filtration [12]. The usual dose is 10 mg/kg three or four a times a day. Andersson et al. recommended dose reduction of TA in patients with renal impairment as follows: for serum creatinine of 120–250 μmol/L 10 mg/kg intravenously twice daily; for serum creatinine of 250–500 μmol/L 10 mg/kg intravenously once daily; for serum creatinine above $\geq$500 μmol/L 10 mg/kg intravenously every 48 hr [12]. Similar doses have been successfully used in dialysis patients with upper GI bleeding [7].

Our patient received a range of TA doses from 15 mg/kg intravenously three times a day to 10 mg/kg once a day orally; all were equally effective. We recommend the use of oral TA in the lowest possible effective dose for the shortest duration to reduce the risk of adverse effects. For our patient this turned out to be 10 mg/kg once a day orally for 3 days. It is possible that TA therapy of less than three days duration might be just as effective but this has not been examined. Early use of TA at home by patients with recurrent hematuria with PCKD would be very cost effective if hospitalization could be prevented.

5. Conclusion

TA can be used safely in some patients with chronic renal impairment and PCKD to treat severe hematuria poorly responsive to conventional therapy. TA dose can be given orally or IV; dose adjustment for renal impairment is important. TA therapy may preserve renal function indirectly in PCKD by avoidance of nephrectomy.

Conflict of Interests

The authors declare no conflict of interests.

Consent

Written consent was obtained from the patient for publication of case.

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