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CASE REPORT

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Tranexamic acid-induced visual impairment in a hemodialysis patient

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Abstract
We report a case of overdosage of tranexamic acid (TNA), which was suggested as the cause of visual impairment in a 56-year-old man. He had been undergoing chronic hemodialysis for 1 year, following 10 years of peritoneal dialysis. He had been hospitalized for an emergency operation for a bleeding ulcer of the stomach and duodenum. After the operation, he experienced a gradual loss of sight over about 1 week, although his general condition was good. He received intravenous injections of TNA as a hemostat during hospitalization for the operation. Two weeks after the operation he became blind. Retinography was flat and his visual field had become narrowed. On fluorescein angiography, microgranular hyperfluorescence, which indicated malfunction of the pigmented layer of the retina, was observed. No abnormality of the brain or the optic nerve was shown by magnetic resonance imaging. Concentrations of vitamins and trace minerals in the blood were within the normal ranges. Administration of vitamins A and B_{12} did not improve his sight. However, discontinuation of TNA rapidly restored his sight, within a few days. He had received TNA once before because of bleeding ulcer, and his sight had been impaired at that time. Based on the repeated episodes, it was strongly suggested that an overdose of TNA in this dialysis patient caused the sight disturbance. Because TNA is metabolized by the kidney, caution is necessary when prescribing TNA for patients with renal failure.

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Introduction

Tranexamic acid (TNA) was originally developed as an anti-inflammatory drug in 1965 in Japan, and it has been widely used as an antifibrinolytic agent which reduces bleeding that is either induced or sustained by local fibrinolytic activity in the tissues and body fluids. TNA inhibits the activation of plasminogen induced by activators in the tissues and body fluids. TNA has been used for the treatment of upper gastrointestinal bleeding since the early 1970s.[1,2] TNA is eliminated entirely via the kidney, and the dosage should be reduced for patients with renal failure.[3] However, TNA has been used carelessly in renal failure patients with hemorrhage. We report here a case of visual impairment due to overdosage of TNA in a chronic hemodialysis patient.

Case report

A 56-year-old man, undergoing hemodialysis following 10 years of peritoneal dialysis (PD) due to glomerular nephritis, was admitted to hospital because of gastrointestinal tract bleeding. In 1998, because of the failure of peritoneal function, the PD was halted and hemodialysis was commenced. Two months after the hemodialysis had been instituted, ascites with fibrin was observed, and he experienced nausea and vomiting. We diagnosed ileus due to encapsulated peritoneal sclerosis (EPS), according to findings on computed tomography, the properties of the ascites, bacteriological examination of the ascites, and laboratory findings. Prednisolone (PSL) was administered, at 0.6 mg/kg body weight (BW), to treat the EPS. About 2 weeks after the start of the PSL therapy, the ascites had disappeared, and the symptoms of the ileus were gradually attenuated. We tapered the dose of PSL from 0.6 mg/kg BW

to 0.2 mg/kg BW over a 3-month period. One month from the time that the dose of PSL was 0.2 mg/kg, he vomited blood and was examined urgently. Upon hospitalization, he received 10 mg/day of PSL, with 300 mg/day of rebamipide daily. During the previous month, he had not been taking an H2-blocker.

On admission, physical examination was normal, except for pallor and upper abdominal pain, and he did not complain of visual impairment. His blood pressure was 90/60 mmHg, and pulse was 80 beats/min in regular sinus rhythm. Laboratory findings on hospitalization were as follows: hemoglobin, 6.2 g/dl; hematocrit, 19.5%; white blood cell count, 7000/μl; and platelet count, 9.8×10^4/μl. Serum sodium was 136 mEq/l; serum potassium, 6.0 mEq/l; serum chloride, 105 mEq/l; blood urea nitrogen, 152 mg/dl; serum creatinine, 11.2 mg/dl; serum albumin, 3.2 g/dl; and total cholesterol, 184 mg/dl. Liver function was normal. Hemostatis was normal.

He underwent an emergency operation with suture stanching. An intravenous injection of 2000 mg of TNA was given as a hemostat when he was hospitalized, and further TNA injections at this dose were given daily during this hospitalization. His anemia was attenuated (hematocrit, 32.0%) by transfusion, and progression of anemia was not seen after the operation. Body fluid volume was properly controlled and the blood pressure, too, was stable. Nutrition was maintained by total parental nutrition (serum albumin, 3.1 g/dl; total cholesterol, 174 mg/dl).

After the operation, his condition improved gradually, except that he experienced loss of sight. About 2 weeks after the operation, he had become almost blind. No marked change was seen on physical examination (blood pressure, total body fluid, weight, etc). Retinography (electroretinogram [ERG]) was flat (data not shown) and his field of vision became narrow. Using the Goldmann perimeter (GP), it was found that his field of view presented afferent view striction with a central angle of 5°, and he could barely see (Fig. 1). On fluorescein angiography (FAG), microgranular hyperfluorescence, which indicated malfunction of retinal pigment epithelium (RPE), was observed (Fig. 2). No pathological change was seen in the brain or the optic nerve by magnetic resonance imaging. Plasma concentrations of vitamins and trace elements were within the normal ranges. The administration of vitamins A and B_{12} did not improve the impaired vision. Surprisingly, termination of the TNA injections resolved his visual impairment promptly, within a few days. Approximately 10 days after the administration of TNA was stopped, his field of view had improved to normal, according to the V-4-e isoptor, which uses the brightest light by GP (Fig. 1).

Four months before the operation, he had sensed a similar impairment of his vision, when he had received TNA because of a bleeding ulcer. From these two episodes, TNA was suggested as the cause of the visual impairment.

Three years after the current episode, he still had weak sight when he was in dark places. On FAG and ERG, performed 1 year after the hospitalization, the abnormal findings remained.

Discussion

There are few previous studies concerning visual impairment caused by TNA. According to one study of four cases from the Swedish Adverse Drug Reaction Committee in December 1980, the administration of TNA was suggested to have caused visual impairment. TNA is often administered to patients with hypotension and severe anemia due to gastrointestinal bleeding. Because the amelioration of subjective symptoms leads to the termination of TNA administration, there is a possibility that visual impairment caused by TNA may be overlooked or confused with symptoms of hypotension and anemia. In the present study, it was strongly suggested that overdosage of TNA induced the visual impairment in a chronic hemodialysis patient.

TNA is eliminated mainly in urine. In normal volunteers, the clearance of TNA is 110–116 ml/min.[4–7] In patients with renal dysfunction, it is important to adjust the dosage to their micturition ability. Andersson et al.[3] recommended reduction of the use of TNA in renal failure patients. In patients with serum creatinine concentrations of 120 to 250 μmol/l, 10 mg/kg BW of TNA should be administered i.v. twice daily. At serum creatinine concentration levels of 250 to 500 μmol/l, 10 mg/kg BW of TNA should be administered every 24 h, while at serum creatinine concentrations greater than 500 μmol/l, the same dose should be administered every 48 h. However, they did not mention the dosage for chronic dialysis patients. In the chronic hemodialysis patient, it is suggested that the dose of TNA can be reduced to less than 10 mg/kg BW every 48 h.

The present patient underwent hemodialysis, and received 2000 mg of TNA every day for 27 days; the serum concentration of TNA appeared to reach a relatively high concentration. It is suggested that the paropsis was due to the high plasma TNA concentration.

In contrast to the findings of a clinical study, it was clearly demonstrated in animal experiments that dysfunction was shown in the retina after the administration of huge amounts of TNA to rabbits for long periods.[8] The mechanism of the visual impairment caused by TNA is not clear. The FAG findings in our patient showed that the abnormality existed in RPE. In addition, the ERG findings showed that the malfunction of the sensory nerve extended to the gangliocyte from the optic nerve in the retina. On FAG and ERG examinations that were performed 1 year after the operation in the present patient, the abnormal findings remained, which suggests that the fault in the retina was not reversible.

Recently, it was reported that the ultrafiltration volume from the peritoneum increased when TNA was administered to PD patients.[9] Actually, at some hospitals, TNA is prescribed on a trial basis to PD patients.[10] Care is required with respect to the quantity of TNA administered to PD patients, and the subjective symptoms relating to sight also require attention.

Cetraxate hydrochloride (cetraxate), an antiulcer drug, has been converted into TNA. So far, there has been no

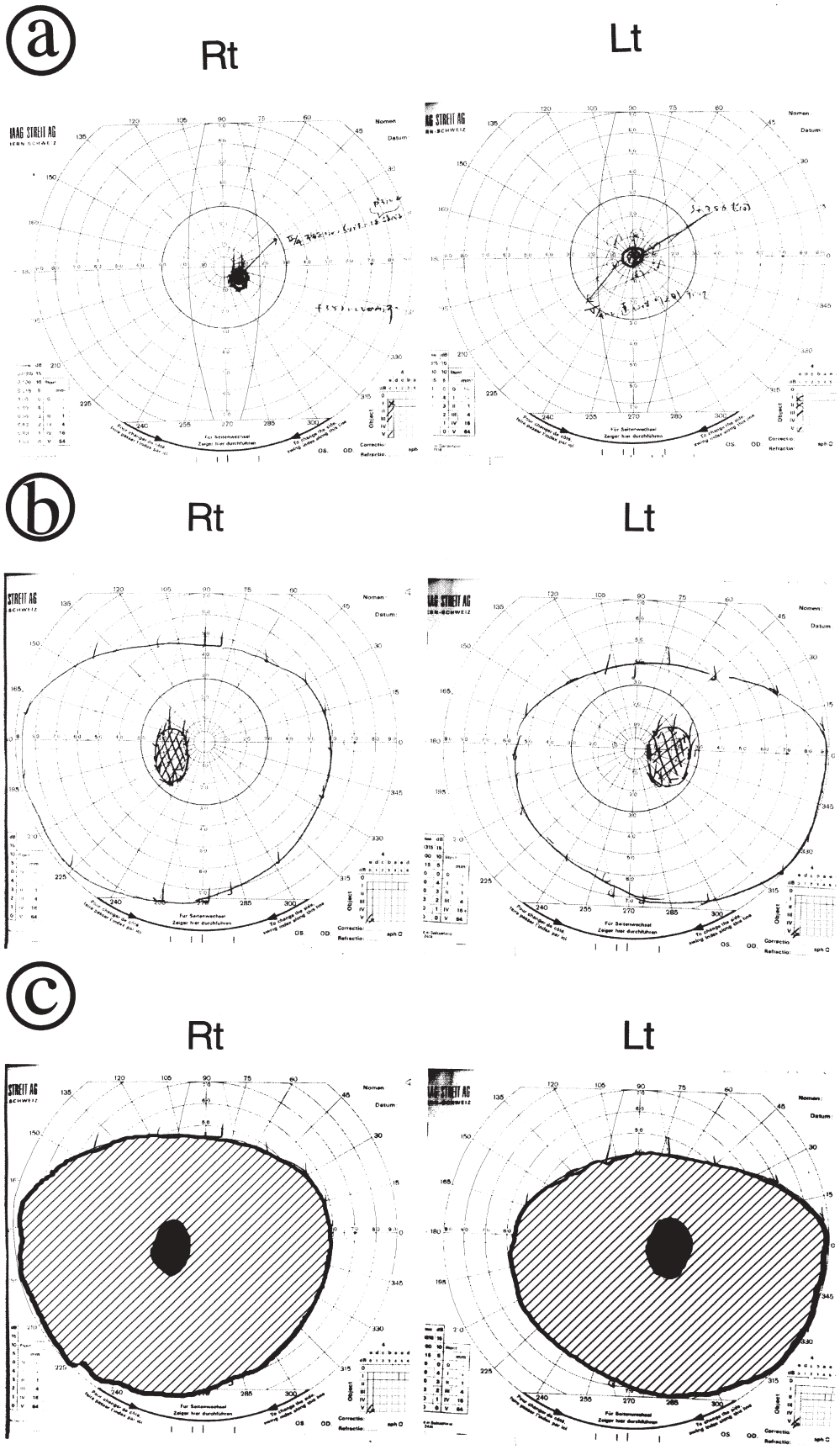

Fig. 1a-c. Change in the field of view checked by the Goldmann perimeter (GP). **a** Shows that the patient's field of view had become very narrow and he was in a condition of total blindness during the time of administration of tranexamic acid (TNA). The writings in the inspection form are comments of the auditor. They mean it was difficult to point out his field of view clearly. **b** Shows the field of view 10 days after the administration of TNA was stopped. According to the V-4-e isoptor, his field of view had improved to normality after TNA administration was stopped. **c** The *hatched area* indicates the range where the patient could see (*hatched area* in **b**). The *black center circles* show Marriott's blind spot. An expansion of Marriott's blind spot can be observed (**b**). *Rt*, right; *Lt*, left

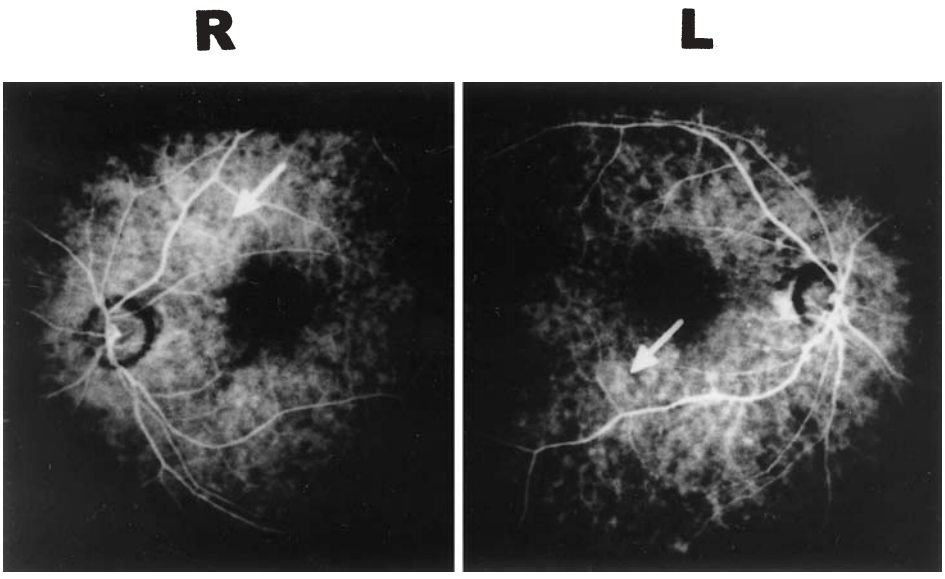

Fig. 2. Fluorescein angiography, performed during administration of TNA. Microgranular hyperfluorescence, which indicated malfunction of the pigmented layer of the retina, is shown (*white arrows*) in both eyes

study of its effects on vision, but cetraxate also requires similar attention in patients with renal failure.

In summary, we reported a case of visual impairment due to over dosage of TNA. Because TNA is mainly excreted from the kidney, attention is required when TNA is administered to patients with renal failure. Guidelines for are required for the use of TNA in dialysis patients.

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