

Anaphylaxis from topical bovine thrombin (Thrombostat[®]) during haemodialysis and evaluation of sensitization among a dialysis population

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Summary

Background Topical bovine thrombin (TBT) is used as a topical haemostatic agent in haemodialysis (HD) units and for surgical procedures. It has caused allergic reactions during surgical procedures, but no previous cases have been reported with dialysis usage.

Objective A case is reported of anaphylaxis due to TBT in an HD patient. This led to a determination of whether HD patients exposed to TBT develop specific IgE and IgG antibodies to TBT and an assessment of the frequency of allergic symptoms in HD patients as compared with peritoneal dialysis (PD) patients.

Methods A cross-sectional study of 100 HD and 52 PD patients was performed using a questionnaire to determine allergic symptoms. An ELISA assay was developed to determine TBT-specific IgE and IgG serum antibodies among HD patients. HD patients without TBT exposure and age- and gender-matched blood donors served as controls.

Results Allergic symptoms temporally related to dialysis reported by a questionnaire were significantly more frequent for HD patients than for PD patients: rhinoconjunctivitis 11% vs. 2%, asthma symptoms 20% vs. 6%, urticaria 23% vs. 8% (P values <0.05). Positive TBT-specific IgE and IgG antibodies were more frequent among 65 exposed HD patients (28% for IgE and 26% for IgG) than for controls (4% and 9%), $P < 0.05$.

Conclusions Results indicate the potential for sensitization and clinical allergic responses to beef thrombin when used for haemostasis in HD and suggest that other haemostatic methods should be considered.

Keywords allergic rhinitis, anaphylaxis, beef thrombin, drug allergy, haemodialysis, urticaria

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Introduction

Topical bovine thrombin (TBT, Thrombostat[®], Parke-Davis, Warner Lambert Company, Pfizer Canada, Kirkland, Quebec, Canada) is a heterologous plasma thrombin of bovine origin that is used as a topical haemostatic agent. It is supplied as a sterile powder, and is applied topically as an aid to haemostasis when blood oozes from capillaries and small venules. It is commonly used to facilitate intra-operative haemostasis for a variety of surgical procedures, as well as to control haemostasis after vascular surgery or access, such as during haemodialysis (HD).

The use of TBT has occasionally been associated with abnormalities in haemostasis, which appears to be related to the formation of antibodies against bovine thrombin and/or factor V, which in some cases may cross-react with human factor V [1]. Dorion et al. [1] identified stored blood samples from patients previously exposed to TBT and compared them with controls. They found that 10% (4.6–15.4%, 95% CI) had antibodies directed against bovine thrombin and other

coagulation factors. Patients receiving multiple exposures were eight times more likely to develop antibodies than were patients with a single exposure ($P < 0.001$).

TBT is also an allergenic substance and has caused sensitivity and allergic reactions, including anaphylaxis [2–4]. Since TBT is a concentrate of bovine plasma thrombin and contains various bovine plasma proteins, the application of this heterologous protein onto broken skin or more invasively can sensitize some people and cause serious adverse reactions.

HD patients may be exposed to bovine thrombin to promote haemostasis during vascular access surgery, and/or by topical usage to prevent oozing from the access following dialysis. A study of 88 HD patients identified IgG or IgM antibodies to bovine thrombin in 31% and found that those with antibodies had significantly more vascular access thrombosis [5], but the study could not determine whether the antibodies caused thromboses or resulted from increased bovine thrombin exposure in those with thrombosis of the vascular access. To date, there have been no reported cases in the literature of IgE-mediated allergic responses to TBT occurring in dialysis units, although the drug is often used in this setting, and the patients are often repeatedly exposed. As a powder, TBT could be aerosolized and patients might be exposed even if the drug is not directly applied to them. It

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would be expected that patients could become sensitized over time.

A case report is presented of a patient undergoing HD who developed anaphylaxis to TBT. In order to identify the extent of this sensitization in HD patients, a survey was performed to assess clinical symptoms of allergy during dialysis and measurement was made of serum Thrombostat[®]-specific IgE and IgG antibodies in this patient population.

Index Case Report

A 40-year-old Filipino woman with end-stage renal disease secondary to IgA nephropathy had undergone thrice-weekly HD since February 1997. She began having difficulties in the dialysis unit in 1998, with an anaphylactic reaction that she attributed to a cleaning solution (Javex[®], Colgate-Palmolive, Toronto, Canada) in the dialysis unit. At the time, she presented with hypotension, shortness of breath, cough, and generalized itching and urticaria. She subsequently had two further episodes, both occurring in the dialysis unit. One of these episodes occurred upon completion of dialysis when TBT (Thrombostat[®]) and Polysporin were being applied to her fistula. In addition to these three episodes, she consistently developed itchy eyes, runny nose and cough within an hour or two of arriving at the dialysis unit. Occasionally, she complained of concurrent generalized itching and urticaria as well. When instructed to spend some time in the dialysis unit on non-dialysis days, she reported the presence of similar symptoms. She denied that these symptoms were present outside the unit.

The patient had no history of allergic rhinoconjunctivitis or asthma, but did have a history of recurrent sinusitis and postnasal drip. She also had a history of hypertension. Her medications included losartan, nifedipine, coumadin, erythropoietin, calcitriol and a multivitamin preparation (Dia-vite). Physical examination during a clinic visit revealed an erythematous nasal mucosa, but no other abnormality. Pulmonary function testing and methacholine challenge were normal (methacholine PC₂₀ > 16 mg/mL). Skin prick testing (SPT) was negative to a natural rubber latex extract (Western Allergy) and further SPTs were performed with polyderm, heparin and Thrombostat[®]. A strongly positive SPT was seen with a saturated solution of Thrombostat[®] in normal saline, causing a 12 × 8 mm weal and surrounding flare. SPT with the same solution on a control subject was negative. The patient had negative SPT responses to heparin and polyderm. An ELISA assay (methods and control groups described below) demonstrated positive IgE and IgG antibodies to Thrombostat[®] in the serum. The cut-off levels (the mean plus two standard deviations of the mean for the optical absorbency of the control group) were 0.621 for IgE and 0.742 for IgG. For the patient, these optical absorbency values were significantly elevated at 1.24 for IgE and 2.12 for IgG.

The patient was advised to receive dialysis in a separate room away from the main dialysis area, since Thrombostat[®] powder might become aerosolized. However, she continued to be symptomatic despite antihistamine use, although her symptoms were milder. Thrombostat[®] was finally removed from the dialysis unit in early 2000, and her symptoms resolved.

Subjects, materials and methods

Patients

Including the index case, a questionnaire was administered to 100 HD and 52 peritoneal dialysis (PD) patients who volunteered to participate at the University Health Network, General and Western Divisions (out of a total patient population of 330 HD and 165 PD patients treated at the hospital during the study period) to assess allergic symptoms during dialysis. The survey was administered to all participants by the same individual over the summer of 2001. Patients were asked questions about the onset and frequency of allergic symptoms (rhinoconjunctivitis, lower respiratory tract symptoms, urticaria, angioedema) during dialysis, and potential Thrombostat[®] exposure (i.e. whether they had received dialysis in the unit during the time period when it was in use) as well as questions as to whether Thrombostat[®] had been used for their own haemostasis in the dialysis unit (i.e. personal use). The majority of HD patients (73%) had Thrombostat[®] exposure. The PD patients had no Thrombostat[®] exposure, and were considered to be controls. Symptoms were only considered relevant if they correlated temporally with dialysis.

Measurement of TBT-specific IgE and IgG antibodies

Sensitization to Thrombostat[®] was determined by the levels of TBT-specific IgE and IgG antibodies, which were measured using an ELISA. Blood samples from the dialysis circuits were taken from 65 HD patients who had been exposed to TBT (including the index case and one patient with probable exposure). Control group blood was obtained from 14 HD patients who had not been exposed to Thrombostat[®], as well as 32 age- and sex-matched blood donors.

An indirect ELISA was developed to measure TBT-specific IgE and IgG antibodies. Optimal conditions were chosen by checkerboard titration. The concentration of Thrombostat[®] extract was 1 µg/mL. Serum dilutions were 1:20 for IgE measurement and 1:100 for IgG measurement. Antibody dilutions were 1:5000 for goat anti-human IgE (P.S. myeloma-affinity purified, a gift from Dr N.F. Adkinson, Jr, The Johns Hopkins Allergy and Asthma Centre, USA); 1:5000 for alkaline phosphatase-conjugated rabbit anti-goat IgG (Jackson ImmunoResearch Laboratories, Inc., West Grove, PA, USA); 1:5000 for mouse anti-human IgG (PharMingen, San Diego, USA); and 1:10 000 for conjugated rabbit anti-mouse IgG (Jackson ImmunoResearch Laboratories, Inc.). Standardization of ELISA results between assays was accomplished by using a reference serum that was obtained from the index case with a high value of Thrombostat[®]-specific IgE and IgG antibodies.

The assay was performed using routine methods as previously described [6]. Briefly, microplates coated with the Thrombostat[®] extract were incubated with test samples or the reference and then incubated with goat anti-human IgE or mouse anti-human IgG. Colour was developed by the addition of alkaline phosphatase-conjugated rabbit anti-goat IgG or conjugated rabbit anti-mouse IgG followed by substrate. Optical absorbency at 405 nm was read, using the Power Wave, Microplate Scanning Spectrophotometer (Bio-Tek Instruments Inc., Winooski, VT, USA). Both IgE and

IgG determinations were performed on two wells and normalized against the reference serum. The results were expressed using optical density. The cut-off level for sensitization to Thrombostat[®] was calculated as the mean optical absorbency of the control group plus two standard deviations.

Statistical analyses

All data were analysed with the Statistical Analysis System statistical package for the PC (SAS Institute, Inc., Cary, NC, USA). Responses were compared on the basis of treatment (HD vs. PD), sensitization to Thrombostat[®], and exposure to Thrombostat[®] for HD patients. Chi-square tests were used to analyse categorical data (with Yates correction for small numbers per cell) and Student's *t*-tests were used for continuous data.

Ethics approval

Ethics approval for this study was obtained from the University Health Network (Toronto, Canada), Research Ethics Board.

Results

One hundred HD patients and 52 PD patients were surveyed by a questionnaire. The average age of HD patients (58.3 years) was not significantly different from PD patients (55.5 years) ($P = 0.33$). The HD group had a greater percentage of male patients compared with the PD group (HD = 63%, PD = 46%, $P = 0.05$). The average number of years spent on dialysis was not significantly different (HD = 4.3 years, PD = 4.2 years, $P = 0.888$).

Allergic symptoms that were not temporally related to dialysis were not significantly different in frequency between

HD and PD patients (Table 1). However, symptoms consistent with allergic responses temporally related to dialysis were reported more frequently in HD patients. Eleven percent of HD patients vs. 1.9% of PD patients experienced symptoms of rhinoconjunctivitis during dialysis (Fisher's exact test $P = 0.05$). Similarly, a significantly greater percentage of HD patients experienced wheezing and shortness of breath (HD = 20.2%, PD = 5.8%, $P = 0.02$) and hives/rashes (HD = 23.2%, PD = 7.7%, $P = 0.02$) during dialysis compared with PD patients (Table 1). There was no significant difference between the two groups for symptoms of swelling or general itchiness related to dialysis. A significantly greater percentage of HD patients experienced any one of the above allergic-type symptoms (HD = 68.7%, PD = 26.9%, $P = 0.002$) or two or more of the above allergic-type symptoms (HD = 16.2%, PD = 1.9%, $P = 0.009$) during dialysis compared with PD patients. Patients who had one, two or more allergic-type symptoms during dialysis were younger than those who did not (2+symptoms = 44.6 years, <2 symptoms = 60.8 years, $P = 0.001$).

Blood serum samples were obtained from 65 HD patients potentially exposed to Thrombostat[®], 14 HD controls (no Thrombostat[®] exposure, i.e. they had not undergone dialysis when it was used in the unit) and 32 age- and sex-matched blood donor controls. In the exposed patient group, positive IgE and IgG antibodies were significantly more common than in the control groups ($P < 0.01$ and $P < 0.05$ for IgE and IgG antibodies, respectively, Fig. 1). Eighteen (27.7%) out of 65 exposed HD serum samples had elevated levels of Thrombostat[®]-specific IgE antibody and 26.2% (16 out of 65) had elevated levels of Thrombostat[®]-specific IgG antibody. In the control groups, consisting of the blood donors and unexposed HD patients, 4.3% (two out of 46) had positive levels of IgE antibody and 8.7% (four out of 46) had positive IgG antibodies to Thrombostat[®] (including both with positive IgE antibodies). The mean optical densities for TBT-specific

Table 1. Comparison of haemodialysis and peritoneal dialysis population characteristics

	Haemodialysis	Peritoneal dialysis	<i>P</i> -value
Number of patients	100	52	
Age (mean $\pm$ SD)	58.3 $\pm$ 16.4	55.5 $\pm$ 16.4	0.33
Years on dialysis (mean $\pm$ SD)	4.3 $\pm$ 5.1	4.2 $\pm$ 5.2	0.89
Male (%)	63.0	46.0	0.05
<i>Symptoms (not specific to dialysis)</i>			
Rhinoconjunctivitis (itchy/runny nose or eyes) (%)	37.4	28.9	0.30
Chest symptoms (wheeze and shortness of breath) (%)	20.3	28.9	0.96
Urticaria (rash or hives) (%)	29.6	21.2	0.27
Angioedema (swelling) (%)	11.2	15.4	0.47
General itch with no urticaria (%)	10.1	25.0	0.02
Any of the above allergic symptoms (%)	66.7	73.1	0.42
<i>Symptoms specifically during dialysis</i>			
Rhinoconjunctivitis during dialysis (%)	11.1	1.9	0.05
Chest symptoms specifically during dialysis (%)	20.2	5.8	0.02
Urticaria specifically during dialysis (%)	23.2	7.7	0.02
Angioedema specifically during dialysis (%)	10.1	11.5	0.79
General itch with no urticaria, specifically during dialysis (%)	4.0	0.0	0.14
Any allergic symptoms specifically during dialysis (%)	68.7	26.9	0.002
Two or more allergic symptoms during dialysis (%)	16.2	1.9	0.009

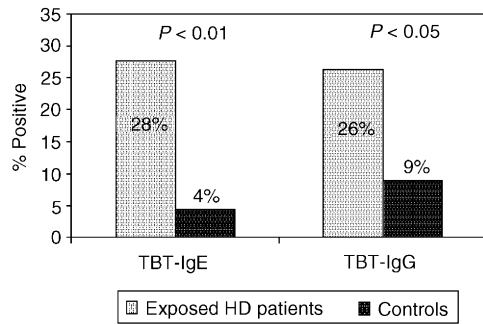


Fig. 1. Percentage of positive Thrombostat[®]-specific IgE and IgG antibody levels among 65 haemodialysis patients exposed to Thrombostat[®], and 46 controls (patients not exposed to Thrombostat[®] and blood donors).

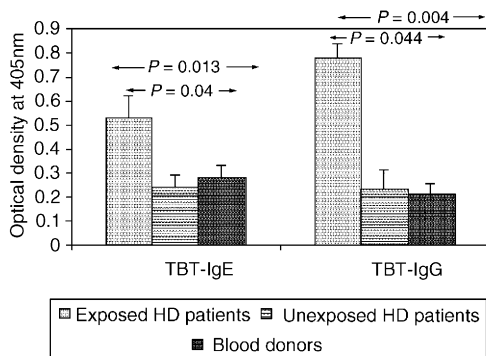


Fig. 2. Distribution of Thrombostat[®]-specific IgE and IgG antibody levels among haemodialysis patients exposed to Thrombostat[®], patients not exposed to Thrombostat[®] and matched blood donors.

IgE and IgG antibodies were significantly higher in the serum of the 65 exposed HD patients compared with the 32 blood donors and the 14 unexposed HD patients (Fig. 2). All but three of the exposed HD subjects with elevated IgE antibodies to Thrombostat[®] also had positive IgG antibodies, and, conversely, all but two exposed HD subjects with elevated IgG antibodies to Thrombostat[®] also had positive IgE antibodies. Among 18 exposed patients with positive Thrombostat[®] IgE antibodies, 11 reported direct personal use of Thrombostat[®] in the dialysis unit (48% of the 23 reporting direct use of Thrombostat[®]). One with positive IgE and IgG antibodies was from the control group who started dialysis in the unit after discontinuation of Thrombostat[®]. The total of 17 exposed patients with positive Thrombostat[®] IgG antibodies included 12 (52%) of those with known personal use of Thrombostat[®].

The average number of years spent on dialysis was significantly higher for patients with high levels of Thrombostat[®] IgE (sensitized 8.3 years, non-sensitized 3.4 years, $P = 0.003$) and IgG (sensitized 8 years, non-sensitized 3.7 years, $P = 0.0023$) (Table 2). Symptoms of rhinoconjunctivitis in the dialysis unit were more common among HD patients with positive IgE antibodies to TBT than among those without IgE antibodies to TBT: 26.3% vs. 6.9%, respectively ($P = 0.04$). Nevertheless, subjects with symptoms consistent with other allergic manifestations in the dialysis unit were not significantly more likely as a group to have TBT-specific antibodies than those without such symptoms (data not shown).

Table 2. Comparison of patients with and without elevated IgE or IgG antibodies to Thrombostat[®]

	Patients with elevated IgE (n = 19)	Patients without elevated IgE (n = 60)	P-value
Number of years on dialysis (mean $\pm$ SD)	8.3 $\pm$ 6.2	3.4 $\pm$ 4.4	0.003
Exposure to airborne Thrombostat [®] (%)	94.7	71.6	< 0.05
Direct use of Thrombostat [®] (%)	57.9	20	< 0.01

	Patients with elevated IgE (n = 18)	Patients without elevated IgE (n = 61)	P-value
Number of years on dialysis (mean $\pm$ SD)	8.0 $\pm$ 5.8	3.7 $\pm$ 4.8	0.002
Exposure to airborne Thrombostat [®] (%)	94.4	73.8	0.10
Directly used Thrombostat [®] (%)	66.7	18.3	< 0.001

Discussion

Dialysis patients are susceptible to many adverse reactions during dialysis. They are routinely exposed to components of the extra-corporeal circuit such as tubings, the dialyser and other foreign substances related to manufacturing and sterilization of the equipment. Anaphylactoid reactions have previously been attributed to ethylene oxide, acetate, dialysate, contamination (bacteria and/or endotoxin), latex, membrane materials (e.g. AN69) and dialyser reuse. Patients who are atopic, often with eosinophilia, and those on ACE inhibitors have been found to be at increased risk [7–9]. This patient population is also frequently exposed to drugs both for anticoagulation (e.g. heparin) and haemostasis (e.g. topical thrombin), both of which can cause adverse reactions [10].

TBT is an antigenic substance that can cause hypersensitivity reactions. The literature contains many case reports detailing adverse reactions to TBT when used in a number of different situations. Rothenberg and Moy [2] described a 51-year-old man who was undergoing decompressive laminectomy and spinal fusion. Surgical gelatin sponges soaked with TBT were placed at the iliac bone graft to improve haemostasis. Within 2–3 min, the patient developed tachycardia and profound hypotension. ST depression on ECG and urticaria were also noted. Resuscitative efforts were hampered by beta-blocker use earlier in surgery. Pulmonary artery catheter pressures were consistent with anaphylaxis. The patient was treated with intravenous hydrocortisone and famotidine and subsequently stabilized. Serum tryptase was elevated at 6.7 ng/mL (nl < 1 ng/mL), consistent with anaphylaxis. SPTs 4 weeks later showed a positive reaction to TBT (6×6 mm² weal, 9×10 mm² flare), while those for environmental allergens, milk, beef and latex extracts were negative.

TBT is also a component of 'fibrin glue'. Fibrin glue is prepared by combining a mixture of bovine thrombin and calcium chloride with concentrated human fibrinogen. Berguer et al. [3] described two cases in which the application of fibrin glue to deep hepatic wounds resulted in sudden

severe hypotension. One patient sustained an intra-operative cardiac arrest refractory to open cardiac massage and died. The other patient was subsequently resuscitated with fluids and vasopressors. The timing of the application of TBT and the patient's sudden deterioration suggested anaphylaxis caused by TBT, although no diagnostic tests were carried out.

A multicentre monitoring of TBT-induced adverse reactions was conducted in Japan from 1986 to 1989 [4]. Five patients with TBT-induced adverse reactions were identified: three cases of TBT-induced shock and two cases of TBT-induced occupational rhinitis and dyspnoea. One case of shock involved irrigation of the urinary bladder with TBT. The other two cases of shock occurred after application of TBT to skin implants. The two cases of rhinitis and dyspnoea occurred after inhalation of TBT powder by pharmacists. None of these patients had an overt history of beef or milk allergy. The RAST analysis of sera from these patients revealed significantly high anti-TBT IgE titres and suggested that these adverse reactions were mediated by anti-TBT IgE antibody. The RAST-inhibition test demonstrated that the antigenic substance was mainly found in the contaminant rather than in the bovine thrombin itself.

Our index case had anaphylactoid episodes, which occurred while Thrombostat[®] was used in the dialysis unit, and cleared when this was removed from the unit. She had positive TBT-specific IgE and IgG antibodies, indicating that this was a likely cause for her allergic responses. In the follow-up study, the survey revealed that HD patients consistently had more complaints of allergic symptoms compared with PD patients. In addition, a significant proportion of HD patients had positive Thrombostat[®]-specific IgE and IgG antibodies. Inhibition assays were not performed to determine the exact component of Thrombostat[®] to which the specific antibodies were directed and inter-lot variation in allergenicity was not assessed in this study. It is possible that the allergen may have been a bovine antigen contaminant rather than the beef thrombin itself. However, the findings do indicate that this preparation, not uncommonly, leads to TBT-specific IgE antibodies in this patient population, with the potential for life-threatening anaphylactic responses. Patients who had the longest exposure to Thrombostat[®], especially if there was a history of Thrombostat[®] use, had a higher incidence of sensitization and developed higher levels of IgE and/or Thrombostat[®]-specific IgG. Of note, the prevalence of specific IgG antibodies to Thrombostat[®] among exposed individuals in the present study (26%) is similar to that of prevalence of IgG and/or IgM antibodies to TBT reported by Sands et al. [5] (31% of HD patients), although IgE antibodies were not assessed in their study. There are many other potential causes for allergic responses in this patient population, such as antibodies to natural rubber latex or ethylene oxide, as well as frequent use in this population of medications such as beta adrenergic-blocking agents and angiotensin-converting enzyme inhibitors, which may enhance or mimic clinical allergic responses. In addition, pruritus is common in patients with renal failure and may be confused with an allergic response on questionnaire. These multiple factors, which may be present in individual patients, may cause difficulty in attribution of symptoms to a single causative agent and may have accounted for the lack of

statistical association between symptoms consistent with allergy and antibodies to TBT in this haemodialysis population, other than an association with rhinoconjunctivitis. Our index case and serologic findings in the haemodialysis population suggest, however, that allergy to Thrombostat[®] also needs to be considered in the differential diagnosis.

Although in this survey no additional cases of anaphylactic responses to Thrombostat[®] were identified other than the index case, consideration might be given to prophylactic screening of patients likely to have frequent exposure to Thrombostat[®], such as patients in dialysis units where this is used. Those patients who are sensitized should be cautioned against future use of TBT and different methods of thrombostasis used both in the dialysis unit and during further vascular access surgery.

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