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Case Report: Prevention of Apheresis Reactions with Icatibant

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PII: S2213-2198(20)31204-6

DOI: <https://doi.org/10.1016/j.jaip.2020.10.049>

Reference: JAIP 3227

To appear in: *The Journal of Allergy and Clinical Immunology: In Practice*

Received Date: 1 July 2020

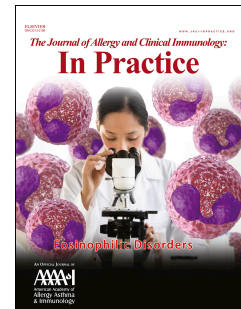
Revised Date: 21 October 2020

Accepted Date: 22 October 2020

Please cite this article as: Kirkpatrick CH, Pirzad A, Case Report: Prevention of Apheresis Reactions with Icatibant, *The Journal of Allergy and Clinical Immunology: In Practice* (2020), doi: <https://doi.org/10.1016/j.jaip.2020.10.049>.

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Case Report: Prevention of Apheresis Reactions with Icatibant

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Word count: 1022

This research did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors.

The authors declare no conflicts of interest.

Clinical Implications:

Systemic reactions during apheresis with dextran sulfate may be due to generation of bradykinin.

These reactions may be prevented by pretreatment with icatibant, an inhibitor of the bradykinin-2 receptor.

Key words:

dextran sulfate

apheresis

bradykinin

angioedema

The familial hyperlipidemias are genetic disorders that are characterized by marked elevations of low-density lipoprotein cholesterol (LDL-C) in the serum.¹ Patients with these disorders are at very high risk for coronary artery disease and xanthomas. In addition to specific diets and weight loss, treatment of these disorders usually consists of statins, aspirin, ezetimibe (an inhibitor of absorption of cholesterol from the small intestine) and evolocomab (a monoclonal antibody that inhibits the *PCSK9* (pro-protein convertase subtilisin/kexin type 9) gene. (Gain of function mutations of this gene are a cause of familial hyperlipidemia). Apheresis treatments circulate plasma or whole blood through adsorbents such as dextran sulfate that remove LDL-C from the plasma.

This case report describes successful management of severe systemic reactions during apheresis in a 36 year old woman with familial hyperlipidemia. Because of her family history, development of xanthomas and laboratory values, she was diagnosed with familial hyperlipidemia at age 5 years. Pharmacologic and apheresis treatments were begun. These were well tolerated.

During her teens, she received oral contraceptives for management of migraine. About this time, she began to have reactions characterized by back pain, hypotension and extreme fatigue during and after apheresis. Approximately 13 years ago, the reactions became more severe with back pain, throat tightness, skin flushing, abdominal cramping that sometimes was associated with nausea and vomiting, and hypotension that required interruption of apheresis and fluid replacement. These symptoms only developed during apheresis; there was no history of angioedema or similar reactions related to trauma, drugs or foods, and there was no family history of similar reactions. In contrast to patients in other reports, she had never taken angiotensin converting enzyme (ACE) inhibitors^{2,3} and she did not ingest turmeric.

Pre-treatment with various combinations of methylprednisolone, dexamethasone, diphenhydramine and ondansetron did not prevent or relieve the symptoms.

Current medications were rosuvastatin, 40 mg daily; ezetimibe 10 mg daily; evolocomab, 420 mg every 30 days; aspirin 81 mg daily and low estrogen (norgestrol 0.3 mg/ethinyl

estradiol (0.03mg) oral contraceptive (prescribed to prevent pregnancy until surgical correction of severe aortic stenosis).

Apheresis was done every seven weeks with the Liposorber LA-15 system (Keneka Pharma America LLC, New York, NY) that uses dextran sulfate cellulose as the adsorbent.

The mechanisms that were considered for the reactions were:

- Activation of kinin generation by dextran sulfate
- Activation of complement
- Anti-dextran antibodies with immune complex formation
- C1 inhibitor deficiency
- Other causes of kinin generation such as those reported in patients with hereditary angioedema with normal C1 inhibitor⁴
- Deficiency of a protease such as angiotensin-converting enzyme

Blood samples were collected six weeks after apheresis and one hour after beginning apheresis (Table I). Notable findings were the slightly low value for C1 inhibitor protein and normal value for C1 inhibitor function and activation of the classical complement pathway with formation of membrane attack complexes (C5b-C9 MAC). She was not deficient in angiotensin converting enzyme. She did not have the mutation in the Factor XII gene that gives the Thr328Lys conversion and is associated with some patients with hereditary angioedema with normal C1 inhibitor.⁵

In consideration of the clinical symptoms, the known exposure to dextran sulfate and the previous report by Davidson and associates, pretreatment with icatibant, an antagonist of the bradykinin-2 receptor, 30 mg subcutaneously, was given 30 minutes prior to apheresis². This completely prevented all of the adverse symptoms and signs. She no longer receives any other pretreatment drugs, and the duration of the apheresis procedure has been reduced from 6-7 hours to 3 hours. After 13 years of adverse reactions, the patient is pleased with this outcome during 10 months of follow up.

Dextran sulfate is a negatively-charged molecule that activates factor XII and the contact pathway to generate bradykinin⁶. Kreiter and associates have shown that production of bradykinin is a common event during apheresis through dextran sulfate columns.⁶ Kinin generation was accompanied by decreases in kallikrein and high molecular weight kininogen (HMWK). Of interest was their observation that, in spite of generation of bradykinin, none of their patients developed adverse symptoms during apheresis. Patients who underwent apheresis with a different system that used heparin-induced lipoprotein precipitation (HELP) instead of dextran sulfate did not have kinin generation. Threshold activation of kinin generation by dextran sulfate has been proposed as a method for differentiation between histaminergic and bradykinin-mediated angioedema⁶.

Treatment with ACE inhibitors is a known risk for development of adverse reactions during apheresis, and these reactions have also been treated successfully with icatibant². A likely predisposing drug in our patient is the estrogen-containing contraceptive that was prescribed for a significant medical reason. Its role in these reactions will be clarified if it can be stopped in the future. High estrogen levels are associated with increased activated Factor XII that converts prekallikrein to kallikrein. Kallikrein, in turn, cleaves HMWK and releases bradykinin.⁸ The clinical effectiveness of pretreatment with icatibant suggests a bradykinin-mediated mechanism for our patient's reactions.

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Table I. Laboratory test results.

Test (normal values)	Results	
	6 weeks after apheresis	1 hour into apheresis
C1 inhibitor (21-39 mg/dL)	20	16
C1 inhibitor function (>41%)	81	84
C4 (19-52 mg/dl)		15
C1q (109-242 µg/ml)		83
C4a (0-2830 ng/ml)	730	3632
CH50 (58-138 U/ml)	101	76
C5b-C9 MAC (95-467 ng/ml)		994
Tryptase – total (1.0-11.4 ng/ml)	6.0	5.5
“ - mature (<1.0 ng/ml)	<1.0	<1.0
ACE (9-67 U/ml)	30	
Factor XII mutation – not found		