

Case Report

Anaphylactoid-Like Reactions in a Patient with HyperLp(a)lipidemia Undergoing LDL Apheresis with Dextran Sulfate Adsorption and Herbal Therapy with the Spice Turmeric

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Elevated Lipoprotein (a) (Lp(a)) levels are associated with atherosclerosis and are independent risk factors for coronary artery disease and stroke [Ariyo et al., *N Engl J Med* 2003;349:2108–2115; Price et al., *Atherosclerosis* 2001;157:241–249]. Low-density lipoprotein (LDL)-apheresis is the most effective therapy for reducing Lp(a) levels [Parker, *Chem Phys Lipids* 1994;67–68:331–338; Stefanutti et al., *Transfus Apher Sci* 2010;42:21–26]. Dextran sulfate-cellulose adsorption (Liposorber[®]) removes both LDL and Lp(a) particles with minimal effect on high-density lipoprotein levels. During the procedure, high levels of bradykinin are generated as the kallikrein-kinin system is activated by contact with the negatively charged dextran-sulfate cellulose [Krieter et al., *Artif Organs* 2005;29:47–52]. Bradykinin is a potent vasodilator and a substrate of the angiotension converting enzyme (ACE). ACE inhibitors are contraindicated for apheresis procedures because these drugs prevent bradykinin degradation, which causes anaphylatoid reactions characterized by hypotension, bradycardia, dyspnea, and flushing [Owen and Brecher, *Transfusion* 1994;34:891–894]. Turmeric is a yellow spice that is used as an herbal remedy to treat a myriad of conditions ranging from abdominal pain to pulmonary infections. Scientific investigations of the ethnomedicinal properties of curcumin, the major derivative of turmeric, suggest that this compound has anti-inflammatory, antioxidant, and antineoplastic properties [Lobo et al., *J Pharm Pharmacol* 2009;61:13–21]. We report a case of a patient undergoing Liposorber[®] therapy for treatment of hyperLp(a)lipidemia who had three episodes of anaphylactoid-like reactions after starting therapy with the spice turmeric. *J. Clin. Apheresis* 00:000–000, 2010. ©2010 Wiley-Liss, Inc.

Key words: LDL-apheresis; Lp(a); turmeric; alternative medicine

INTRODUCTION

Elevated Lipoprotein (a) (Lp(a)) levels are associated with atherosclerosis and are independent risk factors for coronary artery disease and stroke [1,2]. Low-density lipoprotein (LDL)-apheresis is the most effective therapy for reducing Lp(a) levels [3,4]. Dextran sulfate-cellulose adsorption (Liposorber[®]) removes both LDL and Lp(a) particles with minimal effect on high-density lipoprotein (HDL) levels. During the procedure, high levels of bradykinin are generated as the kallikrein-kinin system is activated by contact with the negatively charged dextran-sulfate cellulose [5]. Bradykinin is a potent vasodilator and a substrate of the angiotension converting enzyme (ACE). ACE inhibitors are contraindicated for apheresis procedures because these drugs prevent bradykinin degradation, which causes anaphylatoid reactions characterized by hypoten-

sion, bradycardia, dyspnea, and flushing [6]. Turmeric is a yellow spice that is used as an herbal remedy to treat a myriad of conditions ranging from abdominal pain to pulmonary infections. Scientific investigations of the ethnomedicinal properties of curcumin, the major derivative of turmeric, suggest that this compound has anti-inflammatory, antioxidant, and antineoplastic properties [7]. We report a case of a patient undergoing Liposorber[®] therapy for treatment of

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hyperLp(a)lipidemia who had three episodes of anaphylactoid-like reactions after starting therapy with the spice turmeric.

CASE REPORT

The patient is a 58-year-old man with a significant cardiac history who is not currently taking an ACE inhibitor. The patient underwent his first coronary artery bypass procedure when he was 34 years old. Five years later, the patient was diagnosed with hyperLp(a)-lipidemia. Despite adherence to a controlled diet and treatment with various lipid-lowering drugs, the patient's Lp(a) values remained persistently elevated and his cardiac status continued to decline. Since 1993, this patient has undergone 68 cardiac catheterizations and has had 23 cardiac and carotid stents implanted. In October 1999, the patient underwent his first Liposorber[®] therapy, and since that time, he has presented to our clinic every 2 weeks for treatment. This patient tolerated Liposorber[®] therapy well and without any complaints until December 2009.

LDL-APHERESIS METHOD

Lipid apheresis therapy was performed using the Kaneka MA-03 Liposorber[®] system (Kanegafuchi Chemical Industry, Japan) every 2 weeks. During this procedure, whole blood is applied to a column of polysulphone fibers (Plasmaflow[®], Asahi-Kasei) to separate blood cells from plasma. Plasma is then passed over a dextran sulfate cellulose column to preferentially adsorb apo-B containing lipoprotein, including Lp(a) and LDL from the plasma. Treated plasma is then recombined with the cellular elements of the blood and returned to the patient. For this patient, the volume of plasma treated during each session was 4.5 L. The first 500 mL of plasma volume was run at an inlet rate of 60 mL/min, and the rate was gradually increased to a maximum of 100 mL/min as tolerated. Prior to each treatment, 4.0 units/Kg of unfractionated heparin were administered to the patient to achieve appropriate anticoagulation required for the lipid apheresis procedure. An additional 3.5 units/Kg were given during the course of the treatment to maintain anticoagulation. Heparin was stopped after 3.5 L of blood was processed through the instrument.

Episode 1

The patient presented for his routine 2-week Liposorber[®] treatment. He reported no interval change in health or medications. His preprocedure vital signs were blood pressure 141/85 mmHg, heart rate 52 bpm, and temperature 97.5°F. His treatment was started using the protocol described above and was uneventful until approximately 2 L of plasma was processed. At

this time, the patient began to complain of feeling lightheaded and nauseated. He was noted to be extremely diaphoretic and hypotensive, with a blood pressure of 67/30 mmHg and a pulse of 80 bpm. The procedure was stopped, and the patient was placed in the Trendelenburg position and given IV saline. After receiving a 1.0 L fluid bolus over approximately 5–10 min, the patient stated that he was feeling better, and his blood pressure had increased to 90/50 mmHg. The procedure was resumed with a lowered flow rate of 40 mL/min, but the patient felt immediately unwell, complaining of nausea and lower back pain. The procedure was then terminated and rinseback of extracorporeal blood was begun. During the rinseback procedure, the patient continued to feel unwell, and his blood pressure measured 63/30 mmHg. An additional 1.0 L saline bolus was administered over 5–10 min, and the patient's blood pressure increased to 118/70 mmHg. Rinseback was then completed over the following 15 min. The patient's symptoms resolved, and his vitals were stable upon discharge with a blood pressure of 130/70 mmHg and heart rate of 52 bpm.

Episode 2

Two weeks later, the patient returned to the clinic for Liposorber[®] treatment. He stated that he was feeling well and that he was taking a "steroid taper" for a sinus infection. His preprocedure vitals were blood pressure 126/70 mmHg, heart rate 57 bpm, and temperature of 97.0°F. After 3 L of plasma was processed, the patient began complaining of flank pain and nausea. Again, he was noted to be diaphoretic and tachycardic. Vital signs at this time were a blood pressure of 111/73 mmHg and heart rate of 112 bpm. The procedure was stopped with the expectation of impending hypotension, and the patient was given a 500 mL saline bolus. The patient rapidly responded to saline administration, and his vitals quickly normalized to a blood pressure of 120/72 mmHg and heart rate of 68 bpm. The procedure was then terminated and rinseback completed with no episodes of hypotension or tachycardia, and the patient was discharged home in stable condition.

Episode 3

The patient returned to the clinic 2 weeks later for Liposorber[®] therapy. The preprocedure vitals were blood pressure of 139/89 mmHg, heart rate of 63 bpm, and temperature of 97.6°F. After 3 L of plasma was processed, the patient's face was noted to be red and flushed, and he complained of feeling nauseated. His vital signs were unchanged with a blood pressure of 130/76 mmHg and heart rate of 68 bpm. The procedure was stopped, and the patient received a 500 mL bolus of saline. When the patient's symptoms resolved, the procedure was re-started, and the patient immediately

felt unwell and complained of nausea and lower back pain. At this time, the procedure was terminated for the day. Rinseback was completed without incident, and the patient was discharged with a blood pressure of 131/79 mmHg and a pulse of 68 bpm.

After the third anaphylactoid-like response, the patient was extensively questioned by the apheresis clinical team about any recent changes that may be contributing to this acute onset of adverse reactions to Liposorber[®] therapy after undergoing a relatively benign course of over 250 successful treatments for over 10 years. Though previous inquiries regarding new mediations had focused on those prescribed by his physicians, this conversation specifically asked about any over-the-counter medications, vitamins, and/or supplements that had been started in the past 3 months. During this interview, the patient reported that he had started taking turmeric in November 2009, approximately 1 week before his first untoward reaction to LDL-apheresis. Every morning, the patient described drinking “several spoonfuls” of turmeric dissolved in water with the hope that it would improve his “overall sense of well-being.” The patient agreed to stop taking the turmeric supplement for 2 weeks after which we would again attempt to perform Liposorber[®] therapy. Returning to the apheresis clinic 2 weeks later, he was able to complete the Liposorber[®] procedure without incident though he did complain of mild back pain. As a result of this uneventful treatment, the patient elected not to continue herbal therapy with turmeric. Consequently, he has had not experienced any further adverse events during the subsequent eight biweekly Liposorber[®] treatments.

DISCUSSION

Lp(a) is composed of an LDL particle that is covalently attached to an apolipoprotein called apolipoprotein(a) (apo(a)). Numerous studies have shown that Lp(a) is an independent risk factor for developing atherosclerosis [1,2]. Between 90 and 95% of plasma, Lp(a) levels are determined by the individual’s genetic constitution, and LDL levels are often normal in these patients. Therefore, it is not surprising that traditional lipid-lowering interventions (i.e., controlled diet and pharmacologic compounds) have minimal effect on circulating Lp(a) levels. In addition, there is significant inter-individual heterogeneity in the size of the apo(a) moiety, which contributes to the atherogenic potential of Lp(a). In general, smaller apo(a) moieties correlate with higher circulating Lp(a) levels and more atherosclerosis [reviewed in Refs. 8,9].

LDL-apheresis is currently the most effective therapy for reducing circulating Lp(a) levels [3,4]. The Liposorber[®] system removes LDL and Lp(a) particles by processing plasma through a column comprising

dextran sulfate-derivitized cellulose. The dextran sulfate matrix is negatively charged, and thus, the positively charged apolipoprotein B moiety of both the LDL and Lp(a) particles binds to the column. The Liposorber[®] procedure has a virtually unlimited ability to bind lipoproteins because it utilizes two columns of dextran sulfate, which alternate binding, each alternatively regenerated in real time during the procedure with hypertonic saline. One to 1.5 plasma volumes are routinely processed over a 2–3 hour procedure. The immediate postprocedure decreases in LDL and Lp(a) are 49–75% and 19–70%, respectively. HDL levels are minimally impacted by this method of liposorption with reductions of 4–17% reported [10,11].

Liposorber[®] therapy is generally safe and is well tolerated by most patients. The most common adverse effects are post-treatment bleeding from needle stick sites and vasovagal reactions [11]. An additional anaphylactoid reaction caused by significant increases of bradykinin in patients on concomitant ACE inhibitor therapy has been described [12]. The negatively charged components of the LDL-apheresis system appear to cause contact activation of the kallikrein-kinin system, which results in extreme production of bradykinin. Normally, bradykinin is degraded into inactive fragments by endogenous ACE. However, in the presence of an ACE inhibitor, substantial levels of bradykinin can accumulate causing vasodilation and hypotension in the patient. In addition, ACE inhibitors block the generation of angiotensin II, a potent vasoconstrictor, which may further exacerbate hypotension in the treated patient. Of note, case reports of patients experiencing anaphylactoid reactions who are not taking ACE inhibitors have been published. Individual sensitivities to increased bradykinin levels may account for these reports [5]. Further, such reactions were also reported in patients exposed to heparin contaminated with over-sulfated chondroitin sulfate in 2008 [13]. Importantly, this patient was not taking ACE inhibitors and the heparin used was free of such over-sulfated material.

Turmeric, a spice derived from the plant *curcuma longa*, has a long history as an herbal remedy, particularly in China and India. Traditional claims of Chinese medicine and Ayurveda are that turmeric is useful for treating disorders of the blood, worms in children, leprosy, nausea, and other conditions [see Ref. 7 for review]. Scientific studies of curcumin, the active component of turmeric, have shown that this compound has numerous biological effects including anticancer, anti-inflammatory, antimicrobial, antioxidant, and hypolipidemic activities [14–17]. *In vitro* studies suggest that curcumin may also have vasodilatory properties, which may be mediated by preventing Ca^{2+} influx through vascular smooth muscle or by blocking angiotensin II receptor signaling [18,19]. Curcumin does not have ACE inhibitory effects [20].

The patient described in this report has a significant cardiac history, which has been attributed to hyperLp(a)-lipidemia. Genetic testing to determine the size of his apo(a) moiety has not been performed. Diet and lipid-lowering drug therapies did not significantly reduce the patient's Lp(a) levels. The patient's pharmacologic therapy remains unchanged for the past several years and includes rosuvastatin, fenofibrate, irbesartan, metoprolol, clopidogrel, and aspirin. Previous treatment with niacin was ineffective and not tolerated by the patient. A literature search reveals no known interactions between turmeric and the patient's current medications that may have given rise to his anaphylatoid episodes. However, given the published reports of curcumin blocking angiotensin II receptor signaling and the fact that this patient was also medicated with an angiotensin II receptor antagonist, it is interesting to speculate that the combined effects of these two compounds may result in increased angiotensin receptor blockade.

Since 1999, the patient has undergone biweekly Liposorber[®] treatments in our clinic. Although he has undergone several cardiac interventions since starting LDL-apheresis, the vast majority of these procedures have been revisions to pre-existing lesions. According to the patient's primary clinical team, he has not shown signs of significant new cardiac disease since starting Liposorber[®] therapy. This patient tolerated this procedure without complaint until December 2009, 1 week after beginning treatment with turmeric. At this time, the patient experienced three consecutive anaphylactoid-like reactions during his Liposorber[®] treatments, which resulted in incomplete Liposorber[®] treatments. After cessation of turmeric, the patient has not experienced any additional anaphylactoid-like reactions to date (eight uneventful biweekly treatments). Although the timing of turmeric supplementation and adverse reactions to Liposorber[®] treatment may be coincidental, the fact that the patient is no longer taking turmeric and is now tolerating the procedure strongly suggests that turmeric may have increased the patient's sensitivity to the effects of bradykinin. We propose that turmeric and curcumin be avoided or used with extreme caution in patients undergoing Liposorber[®] therapy. In addition, this case highlights the importance of querying patients about their use of alternative therapies and should serve as a reminder that some natural therapies may be contraindicated when combined with treatments of Western medicine.

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