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Teaching Point
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There's something fishy about this bleeding

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Introduction

Whittier and Korbet reported their experience with percutaneous renal biopsy using real-time ultrasound guidance and a 14-gauge automatic biopsy needle in 750 patients in which 6.4% of patients had a major complication, defined as a complication resulting in the need for blood transfusion, radiographic or surgical intervention, acute renal failure or obstruction, septicemia or death, with 79% of this group requiring blood transfusion. Life-threatening complications were fortunately rare, with a frequency of $<0.1\%$ [1]. Obviously, careful identification of factors that can increase bleeding risk, so they may be avoided, is essential to avoiding hemorrhagic complications.

In addition to reviewing a complete blood count and standard metrics of coagulation such as prothrombin and partial thromboplastin times, preparation for a renal biopsy includes a review of a patient's medications to ensure that potential anticoagulants are discontinued beforehand. Regular ingestion of omega-3 fatty acids, derived from fish oils, should be considered in pre-biopsy screening in light of the propensity of omega-3 fatty acids to impair platelet function. We present a case with the goal of increasing awareness of the antiplatelet properties of omega-3 fatty acids.

Case

A 23-year-old male recipient of a remote bilateral lung transplant for bronchopulmonary dysplasia presented to Johns Hopkins Hospital for an elective outpatient percutaneous renal biopsy to investigate worsening chronic kidney disease. He was taking long-term prednisone and had chronic easy bruising; but on questioning before the biopsy procedure, he related relatively new gingival bleeding and epistaxis. He had started taking 1 g daily of over-the-counter omega-3 fatty acid supplements ~4 weeks earlier. He did not take aspirin, non-steroidal anti-inflammatory agents, or conventional anticoagulants. Prothrombin time, partial thromboplastin time and platelet count were normal. The blood urea nitrogen and serum creatinine were 17.5 mmol/L (49 mg/dL) and 185.6 μmol/L (2.1 mg/dL), respectively. The biopsy was postponed and a platelet function assay (PFA-100®) was performed, using both collagen-epinephrine and collagen-ADP substrates. The closure time using the collagen-ADP assay was normal at 100 s (range 73–118 s); but using the collagen-epinephrine assay, it was elevated to >300 s (range 94–193 s). The omega-3 fatty acids were discontinued, with disappearance of his gingival bleeding and epistaxis within a couple of days and normalization of the closure time using the collagen-epinephrine assay (137 s) when rechecked 10 days later. Percutaneous renal biopsy was performed the following day without complication.

Discussion

The American Heart Association recommends regular ingestion of fatty fish, or use of fish oil supplements, in patients with coronary artery disease or hypertriglyceridemia [2]. Having previously been approved in Europe and Asia for prescription use, in 2004 the US Food and Drug Administration also approved Omacor (renamed Lovaza in 2007), the first prescription omega-3 fatty acid preparation containing highly concentrated ethyl esters of eicosapentaenoic acid and docosahexaenoic acid, as an adjunct to dietary modification in patients with serum triglycerides $\geq$ 5.65 mmol/L (500 mg/dL). Since then, use of Lovaza has steadily soared, with worldwide sales topping $1 billion USD in 2009 (http://www.neptunebiotech.com/corporate/press-releases/271-neptune-reports completion-of-acastipharma-comparative-benchmarking-program-versus-lovaza).

Omega-3 fatty acids also continue to be studied specifically as treatments for various glomerular diseases, including IgA nephropathy, lupus nephritis and membranous nephropathy [3]. Patients with these nephropathies commonly undergo a repeat kidney biopsy at some time during their disease course in order to determine response to therapies and/or to provide current prognostic information.

In addition to being used for specific cardiovascular or nephrologic conditions, omega-3 fatty acids are also taken by many patients without a prescription as a nutritional supplement. It therefore follows that many patients in need of a kidney biopsy may already be taking omega-3 fatty acids, and it is mandatory that nephrologists be cognizant of the potential bleeding risks these medications pose. However, in our experience, it is still not widely appreciated that they impair platelet function. Since the early 1980s, it has been known that omega-3 fatty acids impair hemostasis by inducing a degree of platelet dysfunction [4, 5]. Interestingly, one study implied an association between high perirenal adipose tissue omega-3 fatty acid levels and hemorrhagic stroke in Greenlanders, whose diet contains high amounts of these fatty acids [6].

Omega-3 fatty acids in fish oils diminish platelet aggregation via several mechanisms [7]. *In vitro*, they competitively inhibit the enzyme cyclooxygenase and subsequently diminish thromboxane A2 production from arachidonic acid in platelet membranes, as well as reducing synthesis of platelet-activating factors. Omega-3 fatty acid ingestion in healthy volunteers at doses of 13.8 g daily can alter the balance between prothrombotic and antithrombotic eicosanoids in favor of an antithrombotic state [8].

Despite such biological data, to date, there are no convincing clinical trial data that fish oil ingestion significantly adds to the incidence of bleeding complications. A review of 19 studies in patients undergoing either coronary artery bypass grafting surgery, percutaneous transluminal coronary angioplasty, diagnostic cardiac catheterization or carotid endarterectomy, in which omega-3 fatty acids were studied for possible beneficial effects on either coronary restenosis rates or progression of atherosclerosis, did not find any increased rate of bleeding complications in patients taking omega-3 fatty acids [9]. Most omega-3 fatty acid doses in these studies were between 4 and 6 g daily. It is important to note that in almost all of these studies, patients were concomitantly taking aspirin and sometimes an additional antiplatelet agent. Any additional bleeding risk in such studies imparted by omega-3 fatty acids may have been insignificant on top of the antiplatelet effect already attributable to aspirin and other antiplatelet agents. It is not clear from clinical trial data whether omega-3 fatty acid use alone, in the absence of standard antiplatelet agents, imparts an increased risk of bleeding. The one study reviewed by Harris in which patients were not taking any other antiplatelet agent, a study involving percutaneous coronary angioplasty, did not detect any significant bleeding risks with fish oils, although a significant limitation of this study was that fish oil treatment was not initiated until the day of the procedure [10].

With the goal of minimizing hemorrhagic complications of percutaneous renal biopsy, how can one be certain of adequate platelet function beforehand? Some authors suggest a bleeding time as part of the pre-biopsy evaluation and recommend that an elevated bleeding time ($>$10 min) be corrected with desmopressin prior to biopsy [1]. However, this assay is not commonly available, it is unpleasant for patients, and its utility to predict clinical postoperative bleeding is not clear [11]. There have been no prospective studies evaluating the effect of an elevated bleeding time on complications of percutaneous renal biopsy, though two prospective studies in percutaneous liver biopsy [12, 13] show a five times higher rate of hemorrhagic complications with an elevated bleeding time. The bleeding time is also operator dependent and it lacks optimal sensitivity for detection of platelet abnormalities [14].

Somewhat more practical is the use of the platelet function analyzer (PFA)-100 to assess platelet aggregation by measuring a ‘closure time’, which is the time it takes a small sample ($<$1 cc) of anticoagulated whole blood to form a platelet-plug that completely blocks an aperture as the sample flows (under high shear stress) across a microscopic aperture in a membrane coated with collagen and either epinephrine or ADP [15]. The PFA-100 is also felt to be more sensitive than the bleeding time to detect aspirin-induced platelet dysfunction [16]. The PFA-100 has a higher sensitivity than the conventional bleeding time for platelet dysfunction in von Willebrand disease. In a study of von Willebrand disease, the PFA-100 identified 100% of patients, while the traditional bleeding time assay was normal in one-third [17]. PFA-100 testing is rapid and serves as a point-of-care test where it is available, although its use is still sparse. We were fortunate to have access to one, which clearly demonstrated out patient’s platelet dysfunction using the collagen-epinephrine assay at the time of his ingestion of omega-3 fatty acids, and the subsequent normalization of the collagen-epinephrine closure time after his 10 day abstinence from the fish oils.

In conclusion, despite the lack of firm evidence for increased bleeding complications attributable to the ingestion of fish oils in clinical studies, the wealth of *in vitro* data demonstrating a diminished effect on platelet aggregation makes discontinuation of fish oils prior to a renal biopsy a prudent practice. Some patients may be more susceptible to the platelet-aggregation reduction effect of fish oils than others; the patient in our case clearly had evidence of impaired platelet function and objectively diminished platelet function, both of which were corrected after the fish oils were stopped, even at a dose as low as only 1 g of omega-3 fatty acids per day.

Teaching points

(1) Use of omega-3 fatty acids is likely to increase, driven primarily by the promise of cardiovascular benefit.

(2) Omega-3 fatty acids promote qualitative platelet dysfunction that occasionally may manifest as clinically evident bleeding, as in our patient.

(3) Patients should be specifically questioned about the use of omega-3 fatty acids prior to renal biopsy or other invasive procedures with risk of bleeding, especially since many patients take them without a prescription as a nutritional supplement without including them in their regular medication lists.

(4) Measurement of the closure time with the PFA-100 is a clinically practical method to rapidly assess qualitative platelet function prior to renal biopsy, if clinically indicated and available.

Conflict of interest statement. None declared.

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