Treating hypertriglyceridemia

In their review of hypertriglyceridemia, George Yuan and colleagues advocate “hemodynamic stabilization, cessation of all oral intake, placement of a nasogastric tube and control of metabolic disturbances” to treat triglyceride-related acute pancreatitis.¹ The authors are skeptical about the use of plasma-pheresis because it provides only a transient benefit.

We use a different treatment method (heparin and insulin infusions to stimulate lipoprotein lipase activity and therefore reduce serum triglyceride levels²)

Figure 1: Serum of a patient with triglyceride-related acute pancreatitis. Left: Lipemic serum before treatment with insulin and heparin. Right: Clear serum after 5 days of therapy.

as the first-line therapy in our hospital, as described in the following case. A 29-year-old man with an uneventful medical history was admitted to hospital because of severe abdominal pain with a clinical diagnosis of acute pancreatitis. The fasting triglyceride level was nearly 8000 mg/dL at admission. In addition to standard therapy for pancreatitis, an insulin infusion was started at 4 IU/h with glucose substitution as necessary. Low-molecular-weight heparin was also administered. Within 5 days the patient was asymptomatic and his triglyceride level had decreased to 450 mg/dL. His lipemic serum had a milky appearance at admission and a nearly normal clear appearance on day 5 (Figure 1). Case series and case reports describing the treatment of pancreatitis with heparin and insulin have been published,^{3–5} but the efficacy of this treatment method has not yet been well established, presumably because of the lack of controlled trials.

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The review of hypertriglyceridemia by George Yuan and colleagues was quite interesting. We would like to highlight

plasma exchange as another therapeutic option for this condition.¹ Plasma exchange is used to treat a broad spectrum of conditions, and it can serve either as a primary or as an adjunct therapy. Familial hypertriglyceridemia is a category I indication for plasma exchange, as defined by the American Society for Apheresis.² Hypercholesterolemia and hypertriglyceridemia are the most common indications for plasma exchange in European countries.³ In some reports, plasma exchange has been found to be useful particularly in patients who are pregnant, who have severe hypertriglyceridemia, who have acute and recurrent pancreatitis with hypertriglyceridemia or who do not respond to other forms of treatment.

Plasma exchange may reduce triglyceride levels and remove circulating activated enzymes and inflammatory mediators.^{4,5} We evaluated the effectiveness of plasma exchange in 7 patients with severe hypertriglyceridemia. Triglyceride and total cholesterol levels were reduced by 46.1% and 50.8%, respectively, and the patients tolerated the therapy well.⁶

Although the evidence to date is limited, plasma exchange may be used safely and effectively in patients with severe hyperlipidemia who are at risk of acute coronary events and acute pancreatitis.

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I wish to provide evidence-based information to correct statements made in the informative and well-written article by George Yuan and colleagues on hypertriglyceridemia¹ with respect to the potential use of omega-3 fatty acids from fish oils to lower triglyceride levels. The authors state that "daily consumption of 4 g of omega-3 fatty acids, along with restricted energy and saturated-fat intakes, can reduce plasma triglyceride levels by as much as 20%. However, omega-3 fatty acids are rarely effective when used as the sole triglyceride-lowering therapy." An earlier review in *CMAJ* outlined evidence for a pronounced effect upon supplementation with docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA).² Calculations from the 65 intervention trials reviewed by Harris³ indicate that plasma triglyceride levels should be reduced by 25%–30% in people with baseline fasting triglyceride levels of 1.70–2.82 mmol/L who take 3 g of supplemental DHA/EPA (combined) per day as their sole triglyceride-lowering therapy. These effects typically occur within 4 weeks in the absence of any significant change in diet. The American Heart Association states that "for individuals with hypertriglyceridemia, 2 to 4 g of DHA/EPA per day, provided as capsules under a physician's care, are recommended."⁴

A reduction in triglyceride levels of 30% or more with 4 g of DHA/EPA per day may be accompanied by a small but significant (5%–10%) increase in low-density lipoprotein cholesterol levels.³ The indirect determination of low-density lipoprotein cholesterol levels by the Friedewald equation will often yield a small increase whenever triglyceride levels are lowered.

DHA/EPA supplementation should

be considered as an additional therapeutic option for hypertriglyceridemia. It is efficacious, safe in most patients and less expensive than most other therapies for triglyceride management, and patient compliance is usually good.⁵ A recent review concluded that combination therapy with statins and DHA/EPA supplementation has been "consistently shown to be an effective, safe, and well-tolerated treatment for combined dyslipidemia."⁶

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Competing interests: Bruce Holub is Director of Scientific Affairs for the DHA/EPA Omega-3 Institute (www.dhaoomega3.org). Croda Inc., Ocean Nutrition Canada Ltd. and EPAX AS, manufacturers of omega-3 fish oil concentrates containing DHA/EPA, provide support to the Institute. In the past year, Dr. Holub has received a speaker fee from EPAX and from Mead Johnson Nutritionals.

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[Two of the authors respond:]

We appreciate the interest that the correspondents have shown in our review of hypertriglyceridemia.¹ Our comment regarding the relative ineffectiveness of fish oil as monotherapy was provided in the context of the treatment of severe hypertriglyceridemia. We agree with Bruce Holub's comments regarding the efficacy of DHA and EPA for milder presentations of hypertriglyceridemia, and Table 2 of our article reflects this

position. We also accept the potential efficacy of the combination of DHA and EPA with statin drugs in patients with combined hyperlipidemia. However, this combination awaits evaluation in larger prospective controlled studies.

Ifran Yavasoglu and colleagues and Georg Röggl and colleagues report dramatic improvements in severe hypertriglyceridemia associated with the use of plasma exchange and insulin and heparin administration, respectively. We also observed apparently dramatic biochemical improvement associated with heparin infusion.² However, our clinical experience with patients who have serum triglyceride concentrations greater than 20 mmol/L, often accompanied by acute pancreatitis, is that admission to hospital with cessation of oral intake and appropriate intravenous fluid replacement (with or without insulin therapy depending on the presence of hyperglycemia) is typically followed by a rapid reduction in plasma triglyceride levels irrespective of other treatment modalities.

When oral food and fluids are withheld, a clinical rule of thumb is that triglyceride levels decay exponentially with a half-life of approximately 48 hours. This is comparable to the reductions observed by Yavasoglu and colleagues for plasma exchange and by Röggl and colleagues for a combined insulin and heparin regimen. Controlled, randomized studies, although logistically challenging, would be required to define the risk versus benefit to patients with severe hypertriglyceridemia of either plasma exchange or routine infusions of insulin or heparin. Until then, we stand by our position that these modalities should be used sparingly, if at all, in this situation.

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