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Review Article

Drug Treatment of Hypertriglyceridemia in Children

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Abstract

Treatment of severe hypertriglyceridemia aims to treat and prevent complications including acute pancreatitis, mesenteric ischemia, and recurrent abdominal pain. The risk of pancreatitis increases with serum triglyceride levels above 1000 mg/dL. The aim of treatment is the reduction of triglycerides to values less than 1000 mg/dL. The indication of hospitalization should be for patients with symptoms and triglycerides values above 1000 mg/dL. Laboratory evaluation should include lipid, metabolic profile, renal function, electrolytes, liver function, glycemic profile, thyroid hormone and urine type I. Patients with severe hypertriglyceridemia and abdominal pain or pancreatitis should be kept fasting and intravenous hydration. The average fasting time is 48 hours. Insulin activates lipoprotein lipase and thus the lipolytic pathway of plasma triglycerides, facilitating the removal of these particles from the circulation, reducing their serum values. The use of plasmapheresis in children with severe hypertriglyceridemia is rare. Being an invasive procedure, it requires specialized centers. The efficacy of plasmapheresis in rapidly reducing plasma triglycerides is 70%. There are no triglycerides -reducing drugs approved for use in children and adolescents. Even without approval for children and adolescents, some of these drugs are used in the presence of fasting serum triglycerides concentrations above 500 mg/dL. Omega-3-fatty acids (omega-3-FA) can be used as adjuvant therapy when the triglycerides concentration is exceeded at 500 mg/dL. Omega-3-FA reduce the hepatic secretion of VLDL cholesterol and increase the catabolism of chylomicron. A new medication for familial chylomicronemia syndrome has been recently approved for adults in many European and South American countries, volanesorsen, an antisense oligoprotein that inhibits apoprotein CIII, a co-activator of lipoprotein lipase. This brings a lot of hope that can in the future be proved safe for children aswell.

Keywords: Familial Chylomicronemia Syndrome; Hypertriglyceridemia; Lipoprotein Lipase; Omega-3-Fatty Acids; Severe Hypertriglyceridemia; Triglycerides

Abbreviations: FCS: Familial Chylomicronemia Syndrome; HTG: Hypertriglyceridemia; LPL: Lipoprotein Lipase; Omega-3-FA: Omega-3-Fatty Acids; SHTG: Severe Hypertriglyceridemia; TG: Triglycerides

Treatment of acute complications of severe hypertriglyceridemia

The clinical picture of familial chylomicronemia syndrome (FCS) affects children and adolescents, with a higher prevalence in children younger than 1 year of life. With breastfeeding and accumulation of chylomicron in the circulation, severe hypertriglyceridemia (SHTG) and onset of symptoms may develop in a period of days to months. In the age groups less than 1 year, the clinical presentation is heterogeneous. In addition to classic symptoms such as abdominal

pain, irritability may be present, especially during breastfeeding, pallor, fever, nausea, vomiting, diarrhea, low intestinal bleeding, and hypotension. In asymptomatic patients, lipemic serum is one of the diagnostic criteria. Initial clinical examination may be normal or present with abdominal pain, hepatospelnomegaly, lipemia retinalis, and eruptive xanthomas [1-4].

Hospitalization

The indication of hospitalization should be for patients with symptoms and TG values above 1000 mg/dL. In asymptomatic patients, hospitalization should take into account previous episodes of pancreatitis.

Laboratory evaluation

Laboratory evaluation should include lipid, metabolic profile, renal function, electrolytes, liver function, glycemic profile, thyroid hormone and urine type I. Depending on the methodology, SHTG may interfere with electrolyte dosages such as sodium, potassium and chloride, reducing its serum values [5-7]. Similarly, levels of amylase and lipase may be normal, even in the presence of pancreatitis [1]. Abdominal imaging tests are recommended for diagnostic confirmation of acute pancreatitis [1].

Treatment

Fasting

Patients with SHTG and abdominal pain or pancreatitis should be kept fasting and intravenous hydration. The average fasting time is 48 hours [8].

Insulin

Insulin activates lipoprotein lipase and thus the lipolytic pathway of plasma TG, facilitating the removal of these particles from the circulation [9], reducing their serum values. Case reports with insulin use in children with FCS are rare. In patients with or without residual LPL activity, the use of continuous intravenous insulin, dextrose solution and fasting were effective in reducing HTG. As these measures were associated with fasting, it cannot be quantified whether the effect of plasma TG reduction is the result of insulin, fasting or both. The indication of intravenous insulin in FCS should be considered in the presence of acute complications of SHTG and in the risk and benefit of this therapy. Intravenous insulin administered continuously infusion, at 0.1-0.3 units/kg/h, allows easier titration of doses compared to subcutaneous bolus. The risk especially in newborns is hypoglycemia. Concomitant infusion of dextrose along the same intravenous line as insulin infusion is important to maintain euglycemia and ensure endogenous insulin secretion. Blood glucose should be monitored in the blood frequently during insulin infusion. The therapeutic response is observed in the first 24 hours [10].

Plasmapheresis

The use of plasmapheresis in children with SHTG is rare. Being an invasive procedure, it requires specialized centers. Therefore, the indication of plasmapheresis in the pediatric population is restricted to cases of refractory HTG, for treatment and prevention of complications such as acute pancreatitis. There are case reports of newborns with SHTG and acute pancreatitis complicated by lactic acidosis, respiratory distress syndrome, and organ failure where immediate reduction of TG with plasmapheresis was beneficial [11-14]. The use of plasmapheresis in newborns is of great concern due to the potential risks related to the extracorporeal procedure, mainly due to hemodynamic effects and hemorrhagic events. Plasma filtration would be preferred in very young babies because it requires a smaller volume of extracorporeal circulation than plasma exchange, but seems to be less effective in SHTG, as chylomicrons remain trapped in the primary plasma filter because of its larger diameter and high molecular weight [11,15]. Stefanutti et al. reported two cases of SHTG in very young babies successfully treated with plasmapheresis without adverse events. These authors introduced modifications to the standard procedure to minimize risks [16]. The efficacy of plasmapheresis in rapidly reducing plasma TG is 70% [17]. Plasmapheresis can technically be the challenge, depending on the age of the child and the availability of the procedure is quite limited [18].

Exchange transfusion (ET)

Was introduced in the late 1940s and has since been applied to many diseases (such as high levels of unconjugated hyperbilirubinemia in the newborn due to any cause, severe anemia, disseminated intravascular coagulation, neonatal sepsis). It is a common procedure performed by neonatologists [19]. The most common related adverse effects include thrombocytopenia, hypocalcaemia, hyperkalemia, apnea, bradycardia, hypotension and catheter-related complications. The first case report of the use of ET in a patient with less than 1 month of life, with FCS and high risk of pancreatitis, resulted in a significant and immediate decrease in plasma TG levels, without adverse events [20]. This effect is by the procedure itself and possibly by the presence, in transfused blood, of the LPL enzyme released from mononuclear blood cells [21, 22]. The ET procedure should be considered for the treatment of SHTG in infants with FCS in order to decrease the risk of potentially fatal pancreatitis.

Drug treatment

Fibrates are the drugs of choice to treat HTG, but with limited evidence of efficacy and safety in the pediatric population. They are not effective if LPL activity is absent, or with very high plasma TG values. They reduce plasma TG by activation of PPAR-alpha receptors (peroxisome proliferator agonists activated receptor-alpha) and decreased liver production VLDL (very low-density lipoprotein). Fibrates may cause the development of gallstones and are contraindicated in patients with altered renal function [1,24,25]. There are no TG-reducing drugs approved for use in children and adolescents [23]. Even without approval for children and adolescents, some of these drugs are used in the presence of fasting serum TG concentrations above 500 mg/dL.

Omega 3

Omega-3-fatty acids (omega-3-FA) can be used as adjuvant therapy when the TG concentration is exceeded at 500 mg/dL. Omega-3-FA reduce the hepatic secretion of VLDL cholesterol and increase the catabolism of chylomicron. Gastrointestinal side effects among them "fish taste" eructations hinder adherence [26,27]. Pediatric clinical trials with omega-3 do not show significant reduction in TG [28,29].

Volanesorsen

A new medication for FCS has been recently approved for adults in many European and South American countries, volanesorsen, an antisense oligoprotein that inhibits apoprotein CIII, a co-activator of LPL [30,31]. This brings a lot of hope that can in the future be proved safe for children aswell. Inhibition of apoC3 using the antisense oligonucleotide reduces triglyceride levels by up to 77% and rates of pancreatitis while improving well-being.

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Conflicts of Interest

No conflict of interest.

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