Cardiology in the Young

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Severe hypertriglyceridemia associated with everolimus drug-eluting stent placement in an infant

Kuan-Chi Lai[1], Julie A. Brothers[2] and Jason Z. Stoller[1]

[1]Division of Neonatology, Children's Hospital of Philadelphia, Philadelphia, PA, USA and [2]Division of Cardiology, Children's Hospital of Philadelphia, Philadelphia, PA, USA

Brief Report

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Author for correspondence:
Jason Z. Stoller, Children's Hospital of Philadelphia, 3401 Civic Center Blvd, Philadelphia, PA 19104, USA. Tel: 215-590-1653; Fax: 215-590-3051;
E-mail: stoller@email.chop.edu

Abstract

We report a case of severe hypertriglyceridemia associated with an everolimus drug-eluting stent in an infant with pulmonary vein stenosis. We review from current literature the mechanisms by which everolimus may cause dyslipidaemia, pharmacokinetics of everolimus in drug-eluting stents, and treatments of hypertriglyceridemia. This case demonstrates the need to closely monitor serum triglyceride levels after everolimus drug-eluting stent placement in infants.

Everolimus is an inhibitor of mammalian target of rapamycin, which is a serine/threonine kinase involved in cell growth and angiogenesis signalling pathways.[1] Everolimus drug-eluting stents leverage the medication's antiproliferative properties to reduce rates of stent thrombosis.[2] Although drug-eluting stents are now commonly employed in the treatment of coronary artery disease,[2] efficacy and safety data of these stents in relieving pulmonary vein stenosis are scarce in adults[3] and extremely limited in paediatrics.[4,5] We report a case of a premature infant with pulmonary hypertension secondary to bronchopulmonary dysplasia and pulmonary vein stenosis, who developed severe hypertriglyceridemia following everolimus drug-eluting stent placement.

Case report

Our case was a 7-month-old former 31 weeks gestation twin male prenatally diagnosed with coarctation of the aorta and selective intrauterine growth restriction secondary to placental discordance. His head circumference, length, and weight at birth were 27.5 cm (14th %tile), 38 cm (8th %tile), and 1.32 kg (10th %tile), respectively. He underwent surgical repair for his coarctation of the aorta at 5 weeks of life. Follow-up echocardiograms, CT angiography, and lung ventilation–perfusion scans subsequently demonstrated evidence of pulmonary hypertension and progressive, left worse than right, pulmonary vein stenosis. At 4 and 5 months of life, he underwent two separate balloon dilations of both right upper and left lower pulmonary veins, at which time he was found to have complete stenosis of his left upper pulmonary vein. He subsequently underwent a third catheterisation at 6 months of life with recanalisation of the right upper pulmonary vein and drug-eluting stent (XIENCE Alpine^{TM} everolimus-eluting stent 4 mm × 8 mm containing 50 μg of everolimus) placement in the left lower pulmonary vein. At the time of everolimus drug-eluting stent placement, his weight, length, and body surface area were 5.9 kg, 59 cm, and 0.29 m^2, respectively.

Triglyceride levels were monitored as part of a parenteral nutrition/intralipid laboratory monitoring protocol. The triglyceride level was 109 mg/dL 4 days prior to drug-eluting stent placement (not on parenteral nutrition/intralipid) and rose to 199 mg/dL 5 days after stent placement. He received 5 days of parenteral nutrition/intralipid following his stent placement. Subsequently, despite being off parenteral nutrition/intralipid and taking fortified maternal breast milk, his triglyceride level continued to rise and reached a peak of 1191 mg/dL 40 days after stent placement. A low-fat diet of breast milk mixed 1:1 with the medium-chain triglyceride-based formula, Monogen, was initiated at that time, and the triglyceride level gradually trended downward (Fig 1).

Concern for a genetic cause for the hypertriglyceridemia was low given his reassuring lipid panel 3 weeks before drug-eluting stent placement (triglyceride 75 mg/dL, total cholesterol 121 mg/dL, high-density lipoprotein cholesterol 16 mg/dL, and low-density lipoprotein cholesterol 90 mg/dL). At the time of his peak triglyceride level of 1191 mg/dL, his total cholesterol was only mildly elevated at 210 mg/dL. There was also no evidence indicating immature or impaired CYP450 3A4 metabolism as an explanation for his hypertriglyceridemia. CYP450 3A4 enzymes are required for the metabolism of many medications. He tolerated several of these medications, including well-known CYP450 3A4 substrates such as midazolam, sildenafil, and dexamethasone. Our patient was discharged home at 9 months of life on a low-fat diet with breast milk

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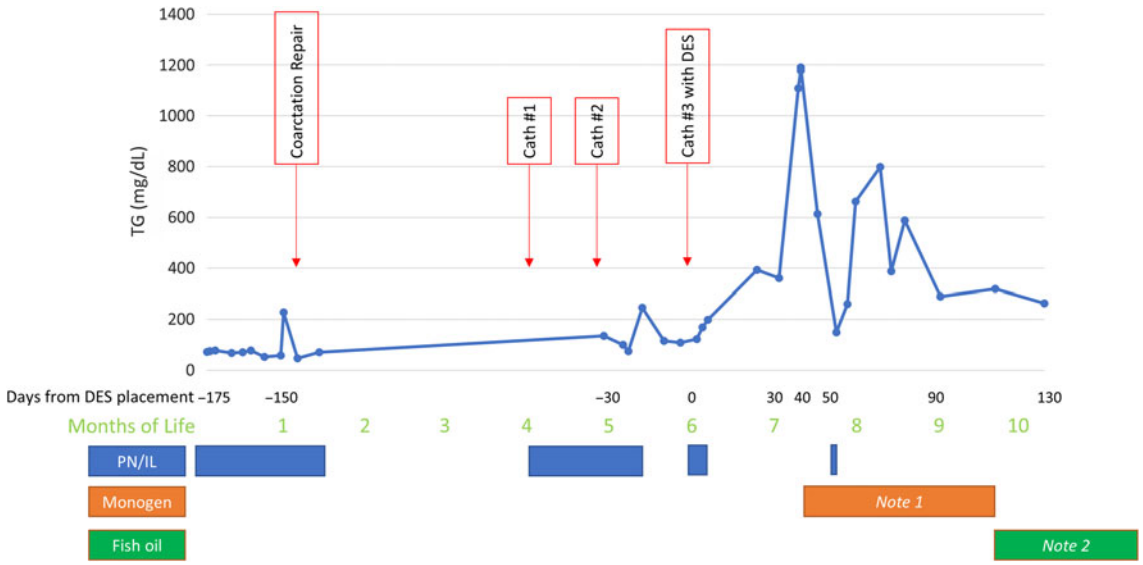

Figure 1. Temporal relationship of triglyceride levels, therapies, and procedures. Baseline normal triglyceride levels peaked 40 days after everolimus drug-eluting stent placement. Triglyceride levels then decreased during supplementation with medium-chain triglyceride-based formula and remained stable after transition to supplementation with a neonatal transitional formula and fish oil. Cath = catheterisation; DES = drug-eluting stent; PN/IL = parenteral nutrition/intralipids. Note 1: 50% maternal breast milk mixed with 50% Monogen. Note 2: 60% maternal breast milk mixed with 40% Neosure, supplemented with daily fish oil.

mixed with Monogen. His triglyceride level remained improved (263 mg/dL) at 10 months of life on a regimen of breast milk mixed with Neosure, supplemented with fish oil. He passed away at 12 months of life due to worsening pulmonary hypertension from his pulmonary vein stenosis.

Discussion

To our knowledge, this is the first report of severe hypertriglyceridemia associated with an everolimus drug-eluting stent in an infant. Oral everolimus, similar to other mammalian target of rapamycin inhibitors, commonly causes dyslipidaemia. Indeed, hypertriglyceridemia has been observed in 40–70% of adult clinical trial patients treated with everolimus for cancer,[1,6] and cases of severe hypertriglyceridemia (>1000 mg/dL) have been reported.[6] The mechanism by which mammalian target of rapamycin inhibitors cause elevated triglyceride levels is poorly understood. *In-vitro* and *in-vivo* studies suggest that mammalian target of rapamycin inhibitors lead to decreased very low-density lipoprotein catabolism and thereby elevated triglyceride levels. The decrease in very low-density lipoprotein catabolism is due to diminished apolipoprotein B100 degradation, decreased activity in lipoprotein lipase, and increased free fatty-acid release from adipose tissues.[1]

Everolimus pharmacokinetics data in the setting of drug-eluting stents are limited. Adult data revealed that peak blood concentrations occurred 10 to 60 minutes after stent placement, $t_{1/2}$ was highly variable and ranged from 45 to 100 hours, and duration of detectable levels was 4 hours to 7 days.[7] The systemic exposure to everolimus drug-eluting stents seems to be well-tolerated in adults as there were no observed cases of increased triglycerides or cholesterol in the SPIRIT family of clinical trials. Unfortunately, there are limited paediatric data available. Our patient's maximal possible everolimus exposure was 0.17 mg/m^2 or 0.008 mg/kg. Everolimus serum levels were not measured because it is not a routine clinical practice. We were therefore unable to estimate the pharmacokinetics in this patient. One case report of an 8-month-old infant who received an everolimus-eluting stent (maximal possible everolimus exposure of 0.4 mg/m^2 or 0.025 mg/kg) to treat pulmonary vein stenosis after repaired total anomalous pulmonary venous return found that everolimus serum concentrations decreased from 0.7 ng/mL at 24 hours to 0.3 ng/mL at 72 hours with no reported short-term side effects.[8] Triglyceride levels were not reported. This patient died 19 days after stent placement so the possible long-term effect on triglyceride levels was unable to be observed, in contrast to our case whose peak triglyceride level occurred 40 days after stent placement. Data on the timing of hypertriglyceridemia as a side effect from everolimus exposure are lacking. There is evidence that the hypertriglyceridemia may persist even after discontinuation of oral everolimus.[6] Furthermore, adult pharmacokinetic studies of everolimus drug-eluting stents showed that the concentration decreased first with a fast distribution/elimination phase followed by a slower elimination phase.[7] This biphasic phenomenon likely represents the initial distribution of everolimus to the tissues followed by elimination from the blood, as well as the continued slow release from the stent. It is estimated that 80% of drug release occurs in the first 30 days.[2] Therefore, we postulate our patient's rising triglyceride levels after stent implantation is a plausible side effect from the sustained low-level exposure to everolimus from the drug-eluting stent.

The specific everolimus-eluting stent used in this patient employed durable polymer coating for drug binding and elution. There is limited literature showing whether biodegradable polymers would have a different drug-release pattern. Pharmacokinetics data of other antiproliferative drugs used in drug-eluting stents such as sirolimus and paclitaxel are also lacking in paediatrics. There is a paucity of efficacy data on drug-eluting stents for the treatment of pulmonary vein stenosis in paediatrics as well. One retrospective study including 57 bare metal stents and 7 drug-eluting stents (sirolimus or paclitaxel) for the treatment of pulmonary vein stenosis in children showed both kinds of stents were effective in the acute relief of stenosis.[5] Occlusion and re-stenosis was common in both groups, but comparison is difficult because of the small number of drug-eluting stents included in the study. Our patient had echocardiographic evidence of stenosis relief for approximately 2 months

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after stent placement (6 mmHg mean gradient across left lower pulmonary vein pre-stent placement improved to 2–3 mmHg mean gradient post-stent placement). However, his mean gradient increased to 11 mmHg at 3 months after initial stent placement, which required another balloon angioplasty. The optimal choice of stents for pulmonary vein stenosis is yet to be established but should be individualised based on the size, length, and location of the stenosis. Therefore, additional trials or registries are warranted to establish the efficacy, pharmacokinetics, and safety of drug-eluting stents in children.

Treatment of hypertriglyceridemia should be tailored to the underlying disorder. In general, dietary restriction and exercise are the first-line management in older children and adults. Pharmacologic therapies including fibrates, nicotinic acid, and omega-3 fatty acids, while effective in lowering triglycerides in adults, have not been approved by the U.S. Federal Food and Drug Administration for use in children, and safe effective doses, notably for infants, are not well-established. Medium-chain triglyceride oil is widely used in the neonatal population for a variety of conditions, such as malnourished premature infants, malabsorption, or familial chylomicronaemia syndrome. Medium-chain triglyceride oil is directly absorbed into the portal system, bypassing the chylomicron transport, and thus does not result in an increased serum triglyceride concentration. Severe symptomatic hypertriglyceridemia can be treated with double-volume exchange transfusion with rapid resolution.[9]

Conclusion

Prospective studies are needed to better elucidate the efficacy, pharmacokinetics, and safety profile of drug-eluting stents in children. The association of hypertriglyceridemia and everolimus drug-eluting stent observed in this case demonstrates the need to closely monitor triglyceride levels after stent placement.

Author ORCIDs. Kuan-Chi Lai 0000-0002-0885-468X

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Conflict of Interest. None.

Ethical Standards. The parents of the case provided informed consent for publication.

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