

Hypertriglyceridemia Induced By L-Asparaginase and Prednisolone in Pediatric Hemato-Oncology: A Case Report

Keywords: Peg L-asparaginase; Acute Lymphoid Leukemia; Hypertriglyceridemia

Abstract

Introduction: L-asparaginase and corticosteroids are widely used in the chemotherapy of acute lymphoblastic leukemia (ALL). This combination is known to cause several adverse effects one of which is hypertriglyceridemia. Although the condition is asymptomatic and reversible it can lead to serious complications.

Case description: This case report of 2-years 6 months old Indian male baby who was on treatment for ALL on day 41 triglycerides levels were 3324mg/dL with no significant symptoms, it was well managed, and the triglyceride levels drop down to 117mg/dL without any complications and interruption in the ongoing treatment.

Conclusion: Combination therapy of L-asparaginase and steroids cause hypertriglyceridemia through various mechanisms leading to various life-threatening complications. However, there are no standard guidelines available to treat drug induced hypertriglyceridemia. Frequent monitoring of serum levels may aid in early diagnosis, prevents complications.

Introduction

L-asparaginase (ASP) has been a key component of the chemotherapy regimens used for acute lymphocytic leukemia (ALL) in children for 50 years. The combination of ASP with polyethylene glycol (PEG-ASP) is a long-acting formulation with a half-life of 6 days which facilitate for intramuscular or intravenous administration [1]. L-ASP and PEG are associated with various adverse effect commonly fatigue, nausea, vomiting, thrombosis, hepatotoxicity, hypersensitivity (clinical and subclinical), pancreatitis, thrombosis, and very rarely hypertriglyceridemia [2]. The administration of asparaginase can cause elevation of the triglyceride levels which is generally seen in around 10% of ALL diagnosed children. Although triglyceride level can hike in the adult patients receiving asparaginase, it occurs most frequently among pediatrics in compared to adults [2,3]. Asparaginase-induced hypertriglyceridemia can be asymptomatic to symptomatic such as it shows symptoms like transaminasemia, pancreatitis, and life-threatening thrombosis or hyper-viscosity syndrome [4]. Nevertheless, most often the condition is reversible and is rarely associated with complications [5]. Here we report a rare case of PEG L-Asparaginase, and steroids induced asymptomatic severe hypertriglyceridemia that is well managed without any complications.

Case Report

A 2-years 6 months old Indian male baby (height 88cm, weight 13.1kg) presented with complaints of bilateral leg pain in the last 6 months, an inability to walk in the past 8 days and pain in abdomen



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from 5-6 days. On laboratory investigation: the complete blood count showed pancytopenia with atypical cells on the peripheral smear, Bone marrow aspiration smear showed 78% blasts with features of acute leukemia (FAB-L1 classification), Marrow flow cytometry showed B-ALL and CALL positive. Further an abnormal karyotyping was observed with t (1:9) (q 21; p13) and I (9) (q 10) trisomy of 9q [hyper diploidy and del (9) (p)] whereas liver function, serum glucose, thyroid function test and serum cholesterol were within normal limits. Considering above findings, Patient was planned to start on protocol 1 A pred (1AP) AIEOP BFM 2017, which includes tablet prednisolone (20mg/m²)10mg PO TID daily [from D1-D28] along with vincristine (1.5mg/m²) 0.8mg IV push with a running NS on a three way and daunorubicin (30mg/m²) 16mg in 100ml NS IV over 1 hour [each four doses- D8, D15, D22, D29], peg-L-Asparaginase (2500IU/m²/dose) 1335 IU in 100ml NS IV over 2 hours i.e., two doses on- D12 & D26. During the therapy, Liver function was assessed before each dose of peg-L-asparaginase and random blood glucose was measured daily. On day 41 blood sample collected in EDTA tubes for routine blood investigation appeared to be milky (Figure 1). Further investigation showed elevated



Figure 1: Milky appearance of blood on D41.

Table 1: Naranjo adverse drug reaction probability scale.

Question	Yes	No	Do not know	Score
1. Are there previous conclusive reports on this reaction?	+1	0	0	+1
2. Did the adverse event appear after the suspected drug was administered?	+2	-1	0	+2
3. Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0	+1
4. Did the adverse event reappear when the drug was readministered?	+2	-1	0	0
5. Are there alternative causes (other than the drug) that could on their own have caused the reaction?	-1	+2	0	0
6. Did the reaction reappear when a placebo was given?	-1	+1	0	0
7. Was the drug detected in blood (or other fluids) in concentrations known to be toxic?	+1	0	0	0
8. Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0	0
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0	0
10. Was the adverse event confirmed by any objective evidence?	+1	0	0	+1
Total score:				5 (probable)

triglyceride level to 3324 mg/dl and Naranjo ADR probability scale used for causality assessment (Table 1). The case was interpreted as possible case of Peg- L- Asparaginase and prednisolone induced hypertriglyceridemia with causality assessment score of 4. Despite of this life-threatening condition, patient triglyceride level gradually fall back to normal within 2 weeks (1st day: 3324 mg/dl, 3rd day: 1458 mg/dl, 14th day: 117 mg/dl) secondary to strict diet modification (<20% low fat diet) without any drug based treatment approach. Patient doesn't experience any complications due to elevated triglyceride. Patient received further treatment and was discharged.

Discussion

Peg-L-asparaginase or L asparaginase is an effective drug in childhood acute lymphoblastic leukemia (ALL) and it has become an important component of most childhood ALL treatment regimens during induction, intensification, and maintenance phases of therapy [6]. It is known that asparaginase in combination with steroids results in massive elevation of triglycerides leading to hypertriglyceridemia. The ADR may be dose dependent or time dependent [7].

Probable mechanisms through which asparaginase and corticosteroid increase triglycerides in the body is through inhibition of lipoprotein lipase i.e., TGs are cleared from the circulation by endothelial cell lipoprotein lipase (LPL), which catabolises TG-rich particles (chylomicrons and VLDL) into fatty acids, and these are then taken up by adipose tissue. Conversely, decreased LPL activity causes elevated serum TGs. Decreased hepatic synthesis of lipoprotein, increased synthesis of VLDL and Increased synthesis of TG rich particles may be another explanation for increased TG levels [4]. On the other hand, corticosteroids are also known as adipokinetic agents which increases triglyceride synthesis and also increases the activity of lipoprotein lipase [7], a key enzyme required for the hydrolysis of triglycerides. When asparaginase and steroids are given together, it is likely that triglyceride-rich lipoproteins are rapidly formed but insufficiently cleared which can cause significant changes in serum lipid levels [6]. Studies revealed that asparaginase inhibits the activity of LPL [3]. If hypertriglyceridemia remains undiagnosed or neglected can lead to severe complications (metabolic syndrome, pancreatitis, stroke, peripheral artery disease, coronary artery disease and carotid artery disease, thrombosis, osteonecrosis) [8], hemophagocytic lymphohistiocytosis [9]. Discontinuation of culprit drug is the prime attempt toward the management drug induced ADR

is discontinuation of drug [10]. It is known that ADR will further increase the treatment burden and may worsen the disease condition [11]. But in our case lack of diagnosis at early-stage lead to drastic increase in TGs levels i.e, 3324mg/dl which is after both the doses of PEG L-Asparaginase. But this case was well managed with strict diet modifications and regularly monitoring TGs levels.

Development of acute pancreatitis indicates severity of the condition and permanently cessation of PEG L-Asparaginase [12]. Even though no standard guidelines on management of asparaginase and steroids induced HTGs till date [7], Very few studies have discussed on this regard. Hoogerbrugge N. et.al, reported similar case of HTG induced by L-asparaginase and corticosteroids. So, the treatment was delayed until plasma TGs levels lowered. Further, while rechallenging of causative drugs to avoid cumulative effects of steroids and asparaginase was given for subsequent doses after steroids was stopped [3]. Studies have also treated the extreme levels of TGs levels with Gemfibrozil 600 mg orally twice daily [2], Gemfibrozil 1200 mg orally per day followed by fish oil 3600mg/day and after 2 weeks fibrates were started [13], IV infusion of SMOFlipid at 0.5 g/kg/day [14], plasmapheresis has been proven to decrease TGs levels within few hours of administration [15].

Kimberly M Lau.et.al, mentioned about treatment recommendations available i.e,

- If TGs < 1000mg/dl, continue asparaginase with frequent monitoring for developing pancreatitis.
- If TGs > 1000mg/dl, recommend withholding asparaginase until TGs levels normalise [2].

However, it is surprising to note that only 10% of the children encounter with hypertriglyceridemia during the treatment of ALL, studies should continue to grow for the exact reason of HTG associated with PEG and corticosteroids leading to any specific mutations. On no account in the previous literature conveyed about L-ASP/PEG serum levels and extent of monitoring this is also a drawback of our study. Moreover, practitioners should routinely do therapeutic drug monitoring (TDM) of the causative drug that helps to guide therapy decisions at early stage [2]. As seen in previous literature therapy decisions were confined to each case basis.

Conclusion

Asparaginase is a lifesaving agent of all pediatric ALL protocols

and is increasingly used to treat patients in combination with various other agents. With many protocols incorporating prolonged and high intensity asparaginase treatment, it is important that practitioners should be aware of all possible treatment-related toxicities. Early diagnosis, frequent monitoring of serum levels and management of asparaginase toxicity will aid in promoting optimal treatment outcomes without any discontinuation of therapy.

List of abbreviations

ADR= Adverse Drug Reaction, ALL= Acute Lymphoblastic Leukemia, ASP= Asparaginase, D= Day, HTG= Hypertriglyceridemia, LPL= Lipoprotein Lipase, PEG =Polyethylene Glycol, TDM =Therapeutic Drug Monitoring, TGs= Triglycerides, TID= Thrice a Day, VLDL= Very Low-Density Lipoprotein.

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