



Anaphylactic reaction to polyethylene-glycol conjugated-asparaginase: Premedication and desensitization may not be sufficient

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Abstract In hypersensitive reactions to native L-asparaginase, either premedication and desensitization or substitution with polyethylene glycol conjugated asparaginase (PEG-ASP) is preferred. Anaphylaxis with PEG-ASP is rare. An 8-year-old girl and a 2.5-year-old boy, both diagnosed as having acute lymphoblastic leukemia, presented with native L-asparaginase hypersensitivity and substitution with PEG-ASP was preferred. They received a premedication (methylprednisolone, hydroxyzine and ranitidine) followed by desensitization with PEG-ASP infusion. Both patients developed anaphylaxis with peg-asparaginase. These are the first reported cases of anaphylactic reaction to PEG-ASP, despite the application of both premedication and desensitization. Anaphylaxis with PEG-ASP is very rare and premedication and desensitization protocols may not prevent these hypersensitive reactions.

Key words anaphylaxis, desensitization, hypersensitivity, polyethylene-glycol asparaginase, premedication.

Acute lymphoblastic leukemia (ALL) is a frequent malignancy in childhood. *Escherichia coli* asparaginase is an important agent in the therapy of ALL, despite the high rates of adverse drug reactions.^{1,2} It has been used in treating leukemia for approximately 40 years. Over the last 20 years, polyethylene glycol conjugated asparaginase (PEG-ASP) has been studied as an alternative form of this agent.³ The frequency of hypersensitivity reactions to native *E. coli* asparaginase ranges between 5 and 45%.^{2,4} The risk increases when the drug is used in higher doses (6000 IU/m²); given in repeated courses of treatment; administered by intravenous route or used as a single agent.⁵ In the case of hypersensitive reactions to native *E. coli* asparaginase, either premedication and desensitization or substitution with *Erwinia* or PEG-ASP is the preferred application.^{2,6,7} Premedication and desensitization protocols may prevent the development of anaphylaxis in many cases.^{6,7} Previously, few cases with PEG-ASP that induced anaphylaxis were reported.^{8–10} However, usage of PEG-ASP even with premedication and desensitization may not be sufficient to prevent severe hypersensitive reactions.

Case reports

Case 1

An 8-year-old girl, diagnosed with Common ALL Antigen (CALLA) (+) B-cell ALL with a central nervous system (CNS) relapse, was admitted for chemotherapy. Previously she was given 11 doses of *E. coli* asparaginase each week. Then 30 weeks after the final dose of *E. coli* asparaginase was given, she had a CNS relapse. At that time she was administered with the same dose of *E. coli* asparaginase with 2-week intervals. As she was experiencing anaphylaxis with native *E. coli* asparaginase, she was injected intramuscularly with the 14th dose 10000 U/m² and we preferred to use PEG-ASP according to the ALL REZ BFM Protocol 2002. Anaphylaxis developed at the 3rd dose of the relapse protocol. A skin-prick test with PEG-ASP (Oncaspar, Sigma-Tau Pharmaceuticals, Gaithersburg, MD, USA) was applied and revealed a positive test response. A previously developed protocol of combined desensitization and premedication was used to administer the PEG-ASP (Table 1).⁷ Premedication with methylprednisolone (2 mg/kg, 4 h before administration), hydroxyzine (1 mg/kg, 13, 7 and 1 h before administration) and ranitidine (1 mg/kg, 1 h before administration) was administered. This was followed by desensitization with the administration of a 2-h PEG-ASP infusion (1000 U/m²) starting with 1 IU and doubling the dose every 10 min until the desired amount was reached. Forty minutes after the initial dose of infusion was administered, pruritus, generalized urticaria, dyspnea and hypotension occurred. Treatment with epinephrine, bolus IV fluid and corticosteroids rapidly reversed the anaphylactic

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Table 1 Desensitization protocol used to administer PEG asparaginase in the first patient in this report⁷

STEP	Bottle number	Infusion time (min)	Total infusion time (min)	Dose given at each step (unit)	Infusion concentration	Volume given at each step	Total dose (unit)
1	1	10	10	1	1 U/1 cc	1 cc	1
2	1	10	20	2	1 U/1 cc	2 cc	3
3	1	10	30	4	1 U/1 cc	4 cc	7
4	1	10	40	8	1 U/1 cc	8 cc	15
5	1	10	50	16	1 U/1 cc	16 cc	31
6	1	10	60	32	1 U/1 cc	32 cc	63
7	1	10	70	64	1 U/1 cc	64 cc	127
8	2	10	80	128	32 U/1 cc	4 cc	255
9	2	10	90	256	32 U/1 cc	8 cc	511
10	2	20	110	512	32 U/1 cc	16 cc	1023
11	2	20	130	402	32 U/1 cc	12.5 cc	1425

reactions of the patient. The family was advised to obtain *Erwinia* asparaginase, however the family was unable to find this drug (it is not sold in Turkey). The chemotherapy of the child for ALL was continued without the asparaginase.

Case 2

A 2.5-year-old boy, diagnosed with CALLA (+) B cell ALL, had grade 2 allergic reactions to native *E. coli* asparaginase administered intramuscularly (at the 5th dose of 10 000 U/m²) so the therapy was switched to PEG-ASP. According to the Modified St Jude T15 Protocol, he was given PEG-ASP (2500 U/m²) intramuscularly. Three hours after the injection of PEG-ASP he developed generalized urticaria, dyspnea, vomiting and hypotension (70/50 mmHg). These anaphylactic reactions were treated with antihistamines and corticosteroids and the patient was followed up for 24 h. The skin-prick test with PEG-ASP that was performed 1 month after the anaphylaxis was positive. Therefore the drug was applied with premedication and desensitization. The above-mentioned premedication and desensitization protocol was applied. He experienced pruritus and generalized urticaria 1 h and 35 min after the desensitization was applied and 1 min after that the child had a cough, dyspnea, tachycardia and mild cyanosis. The drug was stopped; intramuscular epinephrine, diphenhydramine and corticosteroids were administered and within 15 min the child recovered. Afterwards *Erwinia* asparaginase was applied and the chemotherapy was continued without any allergic complications.

Discussion

To the best of our knowledge, the above-mentioned two cases are the first reported cases of anaphylactic reaction to PEG-ASP, despite the application of both premedication and desensitization. Although the hypersensitive reactions to native asparaginase have been well described, anaphylaxis with PEG-ASP is not common and premedication and desensitization protocols are expected to prevent these hypersensitivity reactions.^{2,5,6} However, our cases suggest that premedication and desensitization protocols may not be sufficient to prevent anaphylaxis induced by PEG-ASP.

Despite its well-proven clinical efficacy, the use of native *E. coli* asparaginase has been limited by frequent toxicities like

the development of hypersensitive reactions.^{1–3} Mechanisms responsible for these reactions include endotoxin contamination, complement-mediated reactions, immunoglobulin (Ig) E-mediated hypersensitivity and IgG or IgM mediated sensitivity.¹¹ The most common forms of clinical hypersensitivity are skin reactions like urticaria and angioedema, followed by respiratory symptoms, gastrointestinal symptoms and neurologic symptoms.⁶ Both of the patients developed skin conditions, respiratory symptoms and cardiovascular signs.

The frequency and severity of allergic reactions related with the type of asparaginase depends on the route of drug administration and the time-point of treatment.⁴ In the case of hypersensitivity reactions, substitution of the native *E. coli* asparaginase with *Erwinia* or PEG-ASP is required. PEGylation prolongs plasma retention time and shields the antigenic determinants of the molecule from the immune system without decreasing the clinical efficacy.³ However, substitution of the drug with PEG-ASP does not confirm the safety of the application, as was seen in both of our cases. Therefore premedication with desensitization in all patients allergic to *E. coli* asparaginase may be a reasonable option. Despite the presence of desensitization protocols in the literature, especially for the native *E. coli* asparaginase,^{5,6} we cannot confirm the safety of the application in some cases. Pharmacologic properties of the PEG-ASP are a major limitation in developing more effective desensitization protocols as the drug is expensive and should be used within 2 h following the preparation according to the information provided on the package leaflet for the user (Oncaspar, Sigma-Tau Pharmaceuticals).

As *Erwinia* asparaginase is antigenically different from the other asparaginase formulations, it is expected that the *Erwinia* asparaginase will be tolerated by the majority of individuals despite anaphylactic reaction to PEG-ASP, as observed in Case 2. Wang *et al.* reported that there was cross-reactivity between patient antibodies raised against natural *E. coli* and PEG-ASP but not with *Erwinia* asparaginase.¹² This finding was supported by another study in 2009 and 10 out of 16 tested sera showed cross-immunoreactivity to PEG-ASP, while no reactivity to L-asparaginase derived from *Erwinia* was observed.¹³ In that study, cross-reacting antibodies were also found in the sera of patients with no overt allergic reaction. L-asparaginase may undergo silent inactivation during the re-induction phase of

therapy.¹³ Willer *et al.* showed that in the presence of moderate Ab levels (6.25–200 AU/mL), the switch from native to PEG-ASP resulted in a significant increase of asparaginase activity above the threshold of 100 U/L ($P < 0.05$) and high (>200 AU/mL) Ab levels affected the PEG-ASP activity. *Erwinia* asparaginase activity was not correlated with anti-*E. coli* asparaginase Ab levels. *Erwinia* asparaginase was found to be the best alternative if Ab levels against *E. coli* asparaginase exceed 200 AU/mL.¹⁴ This fact is important with regard to appropriate dosage and enzyme-activity monitoring in patients undergoing repeated treatment with various L-asparaginase preparations is necessary. The absence of cross-reactivity of *E. coli* asparaginase with *Erwinia* asparaginase may be the main reason for the safe use of *Erwinia* asparaginase in Case 2.

Soyer *et al.* described an algorithm for desensitization of patients who have experienced anaphylaxis to L-asparaginase.⁷ We suggest adding another step as an alternative with *Erwinia* asparaginase for patients who had anaphylaxis with PEG-ASP despite the premedication and desensitization.

In conclusion, we report the first two cases of anaphylactic reaction to PEG-ASP despite the application of both premedication and desensitization. Anaphylaxis with PEG-ASP is very rare and premedication and desensitization protocols may not prevent these hypersensitivity reactions as seen in our cases. Furthermore *Erwinia* asparaginase may be an option for patients who have suffered from anaphylactic reactions to *E. coli* asparaginase and PEG-ASP.

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Neonatal pneumoperitoneum and meconium-stained peritoneal fluid of uncertain cause

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Abstract A 2-day-old male infant was referred to hospital because he was continually moaning. Massive pneumoperitoneum was observed on plain radiographs on the day of admission. This case is unique in that the massive

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