Case Report

A 6-Step Desensitization Protocol in a Pediatric Patient with L-asparaginase Anaphylaxis: A Case Report

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Abstract

L-asparaginase (L-asp) is an important chemotherapeutic drug for acute lymphoblastic leukemia. Desensitization is useful in administering medication to patients who have drug-induced anaphylaxis when alternative drugs are not available.

Case: We report a successful case of a 3-year-old Thai boy with L-asp induced anaphylaxis using our 6-step desensitization protocol, with 0.1%, 1%, 5%, 10%, 42%, and the remaining 42% of the total dose of L-asp.

Keywords: Drug hypersensitivity, Anaphylaxis, Desensitization, L-asparaginase

Volume 2023, Issue 1, Page 75-80

https://asianmedjam.com/

Received: 28 June 2021 **Revised: 22 August 2022** **Accepted: 15 September 2022**

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Introduction

Native Escherichia coli (*E. coli*) L-asparaginase (L-asp) is the first-line treatment of acute lymphoblastic leukemia (ALL) in children.[1] Drug hypersensitivity reactions can occur in approximate to 15 - 20% of patients.[2-4] Typically, Erwinia chrysanthemi L-asp is substituted but this is far costlier than native *E. coli* L-asp, and it is unavailable in some countries.[5] Therefore, desensitization for native *E. coli* L-asp may be an appropriate option. We report a successful case of L-asp induced anaphylaxis using our 6-step desensitization protocol.

Case Presentation

A 3-year-old Thai boy with ALL was treated with the standard risk Thai National Protocol 2015 for the induction phase. He had received a total of 6 doses of intramuscular native *E. coli* L-asp 3,300 IU (10,000 IU/m2/dose), without clinical reaction. Since his minimal residual disease (MRD) assay was positive (0.11%) post-induction, we switched to a high-risk augmented consolidation phase.

For the high-risk augmented consolidation phase, L-asp was increased to 25,000 IU/m^2/dose. His body surface area (BSA) was 0.4 m^2. He received a single intramuscular 10,000 IU dose of L-asp during consolidation phase week 3 as scheduled without abnormal clinical reaction.

However, during consolidation phase week 4, he developed anaphylaxis with clinical symptoms of urticaria, expiratory wheezing, and oxygen saturation at 91% after receiving intramuscular 10,000 IU of L-asp for 30 min. He was immediately given a single dose of intramuscular epinephrine. In addition, intravenous corticosteroid and antihistamine were given on the first day of the anaphylaxis episode, and oral corticosteroid and antihistamine were continued for a total of 5 days. Despite anaphylaxis reaction, the patient still required 6 doses of L-asp to complete the high-risk augmented-delay-intensification phase and there was no alternative drug available. Hence, the desensitization of L-asp was applied for the patient.

Methods

Desensitization protocol

Two desensitization protocols: 5-step and 6-step protocol were used for this patient (Table 1 and 2, respectively). Desensitization was performed in the Pediatric Intensive Care Unit under close supervision by physicians and a nurse. Premedication included dexamethasone (2 mg/kg) and chlorpheniramine (CPM) (1 mg/kg) that was given at 1 h before each L-asp infusion.Vital signs were assessed every 30 min during desensitization and 24 h after completion of desensitization. Clinical features of anaphylaxis were assessed throughout the desensitization period and 24 h later. Also, the patient was continuously monitored for abnormal signs and symptoms (e.g., skin rash or vomiting). L-asp (Leunase®) was produced by Kyowa Kirin Co, Ltd.

In the first attempt at desensitization, which was 4 weeks after the anaphylaxis event, we performed a 5-step desensitization protocol as previously published.[3] Single doses each of dexamethasone (2 mg/kg) and chlorpheniramine (CPM) (1 mg/kg) were administered intravenously 1 h before each L-asp infusion as premedication. The protocol was 0.1%, 1%, 5%, 10%, and the remaining 84% of the total dose of L-asp (25,000 IU/m^2). His BSA was 0.4 m^2. The total dose of L-asp was 10,000 IU. We prepared solutions of 10, 100, 500, 1,000, and 8,400 IU in 240 mL 0.9% saline. The intravenous infusions were performed at the rate of 60 mL/h over 4 h (20 h in total) (Table 1). He developed urticaria on his trunk and angioedema on both eyelids when he received the fifth solution at 10 min. He was treated with single doses each of intravenous dexamethasone and CPM. After his clinical symptoms resolved, L-asp was re-administered at a decreased infusion rate of 30 mL/h until the total therapeutic dose was completed.

The second desensitization round was given as scheduled. We again gave premedication and used the same 5-step desensitization protocol as the first round. He developed anaphylaxis with clinical symptoms of tachypnea (respiratory rate 64/min), urticaria, lip angioedema, expiratory wheezing, and reduced oxygen saturation at 88% when he received the fifth solution for 70 min (accumulated L-asp at approximate at 4,000 IU). He was given single doses each of intramuscular epinephrine, nebulized salbutamol, intravenous CPM, and ranitidine. After his clinical symptoms resolved, L-asp was re-administered at a decreased infusion rate of 30 mL/h until achieving the therapeutic dose.

At the third desensitization, we decided to modify the protocol to decrease the final concentration to half the previous protocol. Thus, we divided the total dose into 6 solutions, 0.1%, 1%, 5%, 10%, 42%, and the remaining 42% of the total dose. At this time his BSA had increased to 0.48 m^2. The total dose was then increased to 12,000 IU (25,000 IU/m^2). Subsequently, 12, 120, 600, and 1,200 IU were prepared in 240 mL 0.9% saline and infused intravenously at the rate of 60 mL/h over 4 h for each solution. For the fifth and sixth solutions, 5,040 IU was prepared in 300 mL 0.9% saline and given at 60 mL/h over 5 h (26 h in total) (Table 2). The final concentration was decreased from 35 IU/mL to 16.8 IU/mL. Single doses each of dexamethasone 2 mg/kg and CPM 1 mg/kg were administered intravenously as premedication 1 h before each solution. On this occasion, the patient did not develop any adverse drug reaction.

Our fourth desensitization round was prepared and performed using the same 6-step desensitization protocol as the third. The total dose of L-asp was 12,000 IU. He received the first to fifth solutions without clinical reaction. While receiving the sixth solution at 4 h 40 min (accumulated L-asp of 11,500 IU), he developed an urticarial rash on his face that was far less severe than during the previous desensitization. He was treated with only intravenous CPM and continued with the same infusion rate of L-asp until the total dose was reached.

At the fifth desensitization, we again performed the 6-step protocol (Table 2). However, his BSA had increased to 0.56 m^2. The total dose of L-asp was increased to 14,000 IU (25,000 IU/m^2). Thus, we prepared 14, 140, 700, and 1,400 IU in 240 mL 0.9% saline for the first, second, third and fourth solutions, respectively. The fifth and sixth solutions were prepared as 5,880 IU in 300 mL 0.9% saline. The final concentration was a minor change to 19.6 IU/mL. Single doses each of dexamethasone 2 mg/kg and CPM 1 mg/kg were administered intravenously as premedication 1 h before each solution. Each solution was infused intravenously at 60 mL/h. While receiving the sixth solution at 90 min (accumulated 9,900 IU of L-asp), he developed an urticarial rash only on his left cheek and left ear with one incidence of vomiting. His respiratory rate, oxygen saturation, breath sounds, and blood pressure were normal. However, as a precaution, we administered single doses each of intramuscular adrenaline, and intravenous dexamethasone, CPM, and ranitidine. Upon clinical symptom resolution, L-asp was re-administered at half the previous rate of 30 mL/h for the sixth solution, until the total therapeutic dose was complete. He did not develop any further reactions after restarting the desensitization.

Finally, at the sixth occasion of desensitization, his BSA was the same as at the fifth round. We gave premedication and prepared 6 solutions similar to those of the fifth desensitization. We prepared 14, 140, 700, and 1,400 IU in 240 mL 0.9% saline for first, second, third, and fourth solutions at infusion rates of 60 mL/h for each dose. The fifth and sixth solutions of L-asp 5,880 IU were prepared in 300 mL 0.9% saline and infused at 30 mL/h. On this occasion, no adverse drug reactions were observed.

After the complete high-risk augmented consolidation phase, his minimal residual disease (MRD) flow cytometry assay was undetectable. He attended regular follow-up to receive the scheduled chemotherapy.

Table 1 Five-step desensitization protocol for L-asp

Solution preparation					
Solution	**Total dose (%)**	**Drug (IU)**		**Volume (mL)**	**Concentration (IU/mL)**
1	0.1	10		240	0.04
2	1	100		240	0.42
3	5	500		240	2.08
4	10	1,000		240	4.16
5	84	8,400		240	35
Protocol for desensitization					
Step	**Solution**	**Rate (mL/h)**	**Time (h)**	**Administered dose (IU)**	**Cumulative dose (IU)**
1	1	60	4	10	10
2	2	60	4	100	110
3	3	60	4	500	610
4	4	60	4	1,000	1,610
5	5	60	4	8,400	10,010

Note: BSA was 0.4 m^2 and the total dose was 25,000 IU/m^2.

Table 2 Six-step desensitization protocol for L-asp

Solution preparation					
Solution	**Total dose (%)**	**Drug (IU)**		**Volume (mL)**	**Concentration (IU/mL)**
1	0.1	12		240	0.05
2	1	120		240	0.50
3	5	600		240	2.5
4	10	1,200		240	5
5	42	5,040		300	16.8
6	42	5,040		300	16.8
Protocol for desensitization					
Step	**Solution**	**Rate (mL/h)**	**Time (h)**	**Administered dose (IU)**	**Cumulative dose (IU)**
1	1	60	4	12	12
2	2	60	4	120	132
3	3	60	4	600	732
4	4	60	4	1,200	1,932
5	5	60	5	5,040	6,792
6	6	60	5	5,040	12,012

Note: BSA was 0.48 m^2 and the total dose was 25,000 IU/m^2.

Discussion

A 3-year-old Thai boy with ALL who developed anaphylaxis after receiving intramuscular L-asp was immediately given a single dose of intramuscular epinephrine as first line medication. In addition, intravenous corticosteroid and antihistamine were given as second line medication. The boy had risk factors for developing allergic reaction (e.g., male gender) and was treated with a high dose regimen in which he received L-asp > 6,000 IU/m^2/day.[3,6]

Mechanisms proposed for L-asp reactions include traces of endotoxin contamination, IgE-mediated hypersensitivity, IgG or IgM antibody-mediated reactions, and complement-mediated reactions.[3] Patients who develop a reaction immediately or within 1 h after drug administration with clinical anaphylaxis are most likely suffering an Ig-E mediated reaction. Desensitization is useful in these patients when alternative drugs are not available.

A skin test is an investigation tool for diagnosis in patients who have a history of a suspected immediate type I hypersensitivity reaction. However, desensitization may be considered as the initial step, regardless of any skin tests, because the standardized skin test for L-asp has not been validated and shows high rates of false negatives.[6] Bahadır et al. reported only 2 of 11 cases had positive skin prick test to *E. coli* L-asp.[4] Therefore, we did not perform a skin test for diagnostic confirmation in this case. Moreover, the time from drug exposure to developing the reaction, and the patient's clinical appearance did not leave any doubt as to the diagnosis of immediate type hypersensitivity.

Two previous studies reported desensitization protocols for native *E. coli* L-asp in children. Soyer et al demonstrated a native *E. coli* L-asp desensitization protocol with the first dose of L-asp given as 1 U intravenously and doubled every 10 min until the desired total was reached.[2] However, approximately 25% of the children experienced anaphylaxis again. Akbayram et al used a 5-step desensitization protocol, which was 0.1%, 1%, 5%, 10%, and the remaining 84% of the total dose of L-asp.[3] None of their patients had anaphylaxis. Unfortunately, our patient did experience anaphylaxis under this 5-step desensitization protocol.

Desensitization is drug and dose specific with the risk stratification individualized for each patient. The general idea is to administer lower cumulative drug concentrations than those that provoked a reaction, to promote subthreshold stimulation of mast cells/basophils, induce inhibitory mechanisms, and render these cells hyporesponsive.[7,8] Thus, we hypothesized that decreasing the infusion concentration would lower the cumulative concentration, which had previously triggered anaphylaxis, and it would also perhaps reduce the chances of any reaction. Fortunately, our patient achieved a successful desensitization as he received L-asp until the full therapeutic dose was reached and without recurrent anaphylaxis.[8]

The clear advantage of successful L-asp desensitization is the patient continuing to receive the medication. However, the efficacy is a concern. Patients who exhibited hypersensitivity to *E. coli*-derived asparaginase showed increased levels of anti-asparaginase antibodies, decreased asparaginase half-life, and overall reduction in asparaginase activity compared with patients who did not experience hypersensitivity.[9] Measurements of serum asparaginase activity level are the best and most reliable indicators of asparaginase efficacy. Trough asparaginase activity levels $\geq$ 0.1 IU/mL appear to be a safe target to ensure therapeutic benefit. When the activity levels are < 0.1 IU/mL, the asparaginase preparation should be omitted.[10] Therefore, serum asparaginase activity level should be considered if available.

In conclusion, our 6-step desensitization protocol with premedication appears to be a successful protocol. It is easy to prepare and administer for the desensitization in children with L-asp anaphylaxis. We would like to encourage other physicians to consider this desensitization protocol for unusual cases such as ours.

Ethical Declarations

This study was approved by the Ethics Committee, Faculty of Medicine, Thammasat University (MTU-EC-035/2563).

Acknowledgements

The authors would like to thank Michael Jan Everts, writer/international instructor, Clinical Research Center, Faculty of Medicine, for language editing.

References

1. Egler RA, Ahuja SP, Matloub Y. L-asparaginase in the treatment of patients with acute lymphoblastic leukemia. *J Pharmacol Pharmacother.* 2016;7(2):62-71.
2. Soyer OU, Aytac S, Tuncer A, Cetin M, Yetgin S, Sekerel BE. Alternative algorithm for L-asparaginase allergy in children with acute lymphoblastic leukemia. *J Allergy Clin Immunol.* 2009;123(4):895-899.
3. Akbayram S, Dogan M, Akgun C, Caksen H, Oner AF. A desensitization protocol in children with L-asparaginase hypersensitivity. *J Pediatr Hematol Oncol.* 2010;32(5):187-191.
4. Bahadır A AM RP, Erduran E, Orhan F. Adverse Skin Reactions Caused by L-Asparaginase. Adverse Skin Reactions Caused by L-Asparaginase: *Allergy or infection. . Asthma Allergy Immunol.* 2015;13:130-133.
5. Burke MJ. How to manage asparaginase hypersensitivity in acute lymphoblastic leukemia. *Future Oncol.* 2014;10(16):2615-2627.
6. Ruggiero A, Triarico S, Trombatore G, et al. Incidence, clinical features and management of hypersensitivity reactions to chemotherapeutic drugs in children with cancer. *Eur J Clin Pharmacol.* 2013;69(10):1739-1746.
7. Giavina-Bianchi P, Patil SU, Banerji A. Immediate Hypersensitivity Reaction to Chemotherapeutic Agents. *J Allergy Clin Immunol Pract.* 2017;5(3):593-599.
8. Cernadas JR, Brockow K, Romano A, et al. General considerations on rapid desensitization for drug hypersensitivity - a consensus statement. *Allergy.* 2010;65(11):1357-1366.
9. Burke MJ, Rheingold SR. Differentiating hypersensitivity versus infusion-related reactions in pediatric patients receiving intravenous asparaginase therapy for acute lymphoblastic leukemia. *Leuk Lymphoma.* 2017;58(3):540-551.
10. Van der Sluis IM, Vrooman LM, Pieters R, et al. Consensus expert recommendations for identification and management of asparaginase hypersensitivity and silent inactivation. *Haematologica.* 2016;101(3):279-85.