L-ASPARAGINASE-INDUCED HYPOFIBRINOGENEMIA: A CASE REPORT

BALAJI O, AMITA D, NAVIN P*

Department of Pharmacology, Kasturba Medical College, Manipal, Karnataka, India. Email: navin903@gmail.com

Received: 27 January 2017, Revised and Accepted: 28 February 2017

ABSTRACT

Anticancer therapy is always known to cause various side effects. L-asparaginase used in the treatment of adult T-cell lymphoblastic leukemia is a novel class of drug, an enzyme produced from plants as well as microorganisms except human. It is known to cause various adverse reactions including life-threatening neurological complications and thrombotic disorders. Hence, we report a case of hypofibrinogenemia associated with L-asparaginase in a patient treated for T-cell adult lymphoblastic leukemia.

Keywords: L-asparaginase, Hypofibrinogenemia, Adverse effect, Leukemia.

INTRODUCTION

L-asparaginase is a novel chemotherapeutic agent present obtained from various plants, bacteria, fungus except humans. It is used in the treatment of adult as well as pediatric lymphoblastic leukemia. L-asparaginase enzyme plays a very crucial role in the production of aspartate family of amino acids, namely, threonine, lysine, and methionine. L-asparaginase is known to cause severe thrombotic complications. Hence, we report a case of L-asparaginase-induced hypofibrinogenemia in a 16-year-old male, T-cell adult lymphoblastic leukemia (ALL) patient in a tertiary care hospital in South India.

CASE REPORT

Informed consent was taken from the patient. A 16-year-old male patient diagnosed of ALL of T-cell type on September 09, 2016 was started on September 10, 2016, with injection vincristine 2 mg and injection daunorubicin 64 mg. After completion of the first cycle, the second cycle was started with L-asparaginase on October 02, 2016, at a dose of 16,000 IU/m² along with vincristine and daunorubicin. The latter two drugs were given on the same day once at the dose as used in the first cycle. L-asparaginase was continued, and after 10 days on October 13, 2016, patient’s routine blood investigation revealed a drop in fibrinogen levels to a very low level of 67.6 mg/dl. Other laboratory parameters were normal, and liver function test was also normal. There was no bleeding or thrombotic events, and finally, L-asparaginase was suspected to be the cause, and other causes were ruled out. L-asparaginase was stopped on October 19, 2016, and the patient’s fibrinogen assay returned to normal levels on October 20, 2016 (Table 1).

DISCUSSION

L-asparaginase is a tetrameric protein, and it plays a pivotal role in the hydrolysis of free L-asparaginase enzyme into aspartic acid and ammonia [1]. L-asparaginase enzyme accounts for almost 40% worldwide sale as a potential therapeutic antileukemic agent [2]. It is also used in the treatment of Hodgkin’s lymphoma, chronic lymphocytic leukemia, and melanosarcoma as antineoplastic agent apart being a novel class of drug used in the treatment of adult T-cell lymphoblastic leukemia. Mashbrun and Wriston first isolated L-asparaginase from Escherichia coli, and this kick started the production of this enzyme in large scale for the treatment of leukemia [2].
performed, and a probable causal relationship was ascribed. Severity scale was performed using Hartwig’s scale [9], and adverse reaction was found to be of mild severity. Furthermore, preventability assessment was done as per Thornton’s scale [10], and adverse reaction was found to be not preventable (Table 2).

CONCLUSION

L-asparaginase, a very useful drug in the treatment of leukemia causes many adverse reactions and hypofibrinogenemia, is one among them. Severe hypofibrinogenemia can lead to life-threatening complications in some patients. Hence, proper monitoring of fibrinogen levels using fibrinogen assays is of utmost importance, and further clinical studies can be performed to find the incidence of hypofibrinogenemia associated with L-asparaginase treatment in leukemia patients.

REFERENCES

1. Thandeeswaran M, Mahendran R, Kiran K, Nawa K, Palaniswamy M, Jayaraman A. Screening and production of anticarcinogenic enzyme from Escherichia coli CTLS20: L - Asparaginase. Int J Pharm Pharm Sci 2016;8(3):244-8.
2. Kumar R, Sedolkar V, Triveni A, Kumar M, Shivannavar C, Gaddad S. Isolation, screening and characterization of L-asparaginase producing fungi from medicinal plants. Int J Pharm Pharm Sci 2015;8(1):281-3.
3. Batool T, Makky EA, Jalal M, Yusoff MM. A comprehensive review on L-asparaginase and its applications. Appl Biochem Biotechnol 2016;178(5):900-23.
4. Bolton-Maggs PH, Perry DJ, Chalmers EA, Parapia LA, Wilde JT, Williams MD, et al. The rare coagulation disorders - Review with guidelines for management from the United Kingdom Haemophilia Centre Doctors' Organisation. Haemophilia 2004;10(5):593-628.
5. Roberts HR, Stinchcombe TE, Gabriel DA. The dysfibrinogenaemias. Br J Haematol 2001;114(2):249-57.
6. Besser MW, MacDonald SG. Acquired hypofibrinogenemia: Current perspectives. J Blood Med 2016;7:217-25.
7. Bettigole RE, Himelstein ES, Oettgen HF, Clifford GO. Hypofibrinogenemia due to L-asparaginase: Studies of fibrinogen survival using autologous 131-I-fibrinogen. Blood 1970;35(2):195-200.
8. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther 1981;30(2):239-45.
9. Hartwig SC, Siegel J, Schneider PJ. Preventability and severity assessment in reporting adverse drug reactions. Am J Hosp Pharm 1992;49(9):2229-32.
10. Schumock GT, Thornton JP. Focusing on the preventability of adverse drug reactions. Hosp Pharm 1992;27(6):538.

Table 1: Fibrinogen levels before and after L-asparaginase

| Date              | Fibrinogen levels (mg/dl) |
|-------------------|---------------------------|
| September 30, 2016| 306                       |
| October 04, 2016  | 167                       |
| October 13, 2016  | 67.6                      |
| October 20, 2016  | 208.7                     |

Table 2: Adverse drug assessment

| Scales  | Assessment        |
|---------|-------------------|
| Naranjo’s| Probable          |
| Hartwig’s| Mild severity    |
| Thornton’s| Not preventable  |