L-asparaginase-induced abnormality in plasma glucose level in patients of acute lymphoblastic leukemia admitted to a tertiary care hospital of Odisha

Mousumee Panigrahi, Trupti Rekha Swain, Rabindra Kumar Jena¹, Ashutosh Panigrahi¹

Abstract:

Objectives: The objective of this study was to evaluate any abnormal change in plasma glucose levels in patients treated with L-asparaginase (L-Asp)-based chemotherapy regimen in patients of acute lymphoblastic leukemia (ALL).

Materials and Methods: This retrospective, hospital-based study was conducted in patients of ALL, admitted to the Clinical Haematology Department of a tertiary care hospital of Odisha from August 2014 to July 2015. Indoor records of 146 patients on multi-centered protocol-841 were evaluated for any alteration in plasma glucose level, time of onset of hypo/hyperglycemia, and persistence of plasma glucose alteration.

Results: Twenty-one percent of patients showed abnormal plasma glucose level. Most of these patients developed hypoglycemia and were of lower age group. Most of these patients developed hypoglycemia and were of lower age group, whereas a majority of higher age group patients developed hyperglycemia. In majority of the cases, abnormal glucose developed after three doses of L-Asp. Hypoglycemia subsided whereas hyperglycemia persisted till the end of our observation period.

Conclusions: L-Asp produces more incidences of hypoglycemia than hyperglycemia in a good number of ALL patients towards which clinicians should be more vigilant. However, hyperglycemia persists for a longer duration than hypoglycemia.

Key words: Acute lymphoblastic leukemia, hyperglycemia, hypoglycemia, L-asparaginase

L-asparaginase (L-Asp) is a vital component of multi-centered protocol (MCP) 841 that is most commonly followed in the management of acute lymphoblastic leukemia (ALL) in patients up to 40 years of age. It has been in use for more than 30 years because of its unique pharmacological features and improved treatment outcomes.¹⁻⁴ However, some peculiar adverse effects have been documented with L-Asp due to its biological nature including coagulopathy, acute pancreatitis, allergic reaction, hyperlipidemia, hyperammonemia, hepatotoxicity, and hyperglycemia.⁵⁻⁸ Although literature scan reveals hyperglycemia as the most important metabolic side effect of L-Asp, two anecdotal reports of L-Asp-induced hypoglycemia have also been reported (Tokyo, Japan, and Kashmir, India).⁹,¹⁰ Analysis of important adverse drug reaction (ADR) profile of one drug and trying to find out its in-depth mechanism can help clinicians to develop strategies to prevent and manage the ADR in a planned way. Thus, the present study was designed to identify the nature and incidence of L-Asp-induced abnormal glucose level in a tertiary care setup. The study was designed to study the changes in plasma glucose levels in patients of ALL being treated with L-Asp-based chemotherapy regimen.

Materials and Methods

This retrospective, hospital-based, observational study was carried out from August 2014 to July 2015 after obtaining necessary permission from the Institutional Ethics Committee. Diagnosed ALL patients admitted to the Department of Clinical Haematology of SCB Medical College during the study period being treated with L-Asp-based chemotherapy (MCP 841 protocol) were included for analysis. All newly diagnosed patients of acute lymphoblastic leukemia admitted to a tertiary care hospital of Odisha. Indian J Pharmacol 2016;48:595-8.
indoor patients on induction therapy with the MCP 841 protocol,[1] of either gender and up to 40 years of age, were included in the analysis. Patients on any other drug other than those in the MCP 841 protocol that could have altered the blood glucose levels were excluded from the study. Patients having abnormal plasma glucose level before starting therapy with L-Asp were also excluded from the study. Patients’ bed head tickets were collected from the record section of the hospital. Under the MCP 841 protocol, a patient is on L-Asp intramuscular every other day on days 2–20 of the first induction therapy. Time of onset of hypoglycemia, persistence of plasma glucose alteration, and patient outcome were noted. Fasting plasma glucose (FPG) levels were noted before the start of treatment with L-Asp, on day 6 and day 12 of L-Asp therapy and after the stoppage of L-Asp therapy. Differences in ADR characteristics of native and pegylated L-Asp were also noted and compared. The serum amylase levels of all these patients were estimated to exclude the possible pancreatitis.

Statistical Analysis
Paired sample t-test was applied using MedCalc version 12 © 1993-2013 MedCalc Software bvba (Acacialaan 22,8400 Ostend, Belgium) to compare the FPG of patients before treatment with L-Asp and on day 6 of L-Asp treatment.

Results
Out of the 146 cases included for analysis, 129 were on native L-Asp and only 17 were on pegylated L-Asp. Twenty-one percent of patients showed altered plasma glucose level out of 146 cases (thirty in number). A total of 17 patients developed hypoglycemia (FPG < 65 mg/dL) whereas only 13 patients developed hyperglycemia (FPG > 100 mg/dL). The serum amylase levels of all these patients were normal which showed the absence of pancreatitis. The median age in the hypoglycemia group was 5.5 years which is much less than that in the hyperglycemia group (19.5 years). The male:female ratio was 13:4 in hypoglycemia group and 10:3 in hyperglycemia group [Table 1].

Of patients who were on native L-Asp, 20.9% developed either hypo- or hyper-glycemia. On the contrary, in patients who were on pegylated L-Asp, 17.6% cases developed plasma glucose abnormality. All of them had hyperglycemia (FPG > 100 mg/dL) [Figure 1].

Out of the total thirty patients who developed abnormality in FPG, 56.67% developed hypoglycemia whereas 43.33% had hyperglycemia. In majority of the cases, the ADR abnormality developed after taking three doses of L-Asp in a particular cycle of chemotherapy. The number of patients who developed hypo- and hyper-glycemia after administration of native L-Asp was 17 and 10, respectively. On the contrary, only three patients treated with pegylated L-Asp developed hyperglycemia. None of them had developed hypoglycemia [Table 2].

All patients in hypoglycemic group had normal plasma glucose level before starting the treatment (mean = 77.5 mg/dL). Most of them developed hypoglycemia (mean = 60.6 mg/dL) on day 6 which returned to normal (mean = 67.3) after stoppage of L-Asp treatment. Similarly, patients in hyperglycemia group had a mean plasma glucose of 86.5 mg/dL. On day 6, majority of the patients had a sharp rise of FPG (mean = 235.6 mg/dL). Hyperglycemia persisted even after the stoppage of L-Asp treatment (mean = 121.6 mg/dL). When the mean plasma glucose levels before the start of treatment with L-Asp were compared with the values on day 6 by paired t-test, the P values for the hypo- and hyper-glycemia groups were found to be 0.0012 and 0.0309, respectively. This suggests a statistically significant alteration of FPG [Figure 2].

Discussion
L-Asp, an enzyme, has a wide application in many therapeutic protocols, including ALL. During ALL treatment, glucose levels are routinely monitored because many patients develop hyperglycemia, presumably because of glucocorticoids and L-Asp. Unexpectedly, many of our patients experienced repeated fasting hypoglycemia during induction and maintenance therapy. Since altered FPG level can change the clinical outcome of patients, it was thought imperative to probe the exact course of hypo/hyperglycemia so that appropriate measures can be taken.

L-Asp is an essential component of ALL regimens. Most patients were given native L-Asp and only a few were given pegylated L-Asp, may be due to cost factor. Approximately, one-fifth of the patients on L-Asp therapy developed abnormal plasma glucose levels. Most of the patients who developed hyperglycemia belonged to higher age group (median age = 19.5 years) compared to patients who have developed hypoglycemia (median age = 5.5 years). This may be due to the fact that, in patients with higher age group, pancreatic reserve is less compared to younger age group. However, there is no significant difference between male to female ratio so far L-Asp-induced abnormal plasma glucose levels (hypo- or hyper-glycemia) are concerned.

In this study, normal range of FPG was taken as 65–100 mg/dL. As per the American Diabetes Association 2016 guidelines, FPG 100–125 mg/dL is taken as impaired fasting glucose and >126 is diabetic. Both these categories are under hyperglycemia. Hypoglycemia is taken as <65 mg/dL because research in healthy adults shows that mental efficiency declines slightly
but measurably as blood glucose falls below 65 mg/dL.[12] FPG abnormality was observed in 20.9% of the cases in native L-Asp group whereas only in 17.6% in pegylated L-Asp group. We could find only cases of hyperglycemia in pegylated L-Asp group whereas incidences of both hypoglycemia and hyperglycemia were observed in native L-Asp-treated group. Almost all the patients developed statistically significant abnormal glucose level after 3rd dose of L-Asp which may be due to the fact that the destruction of the endocrine pancreas is dose-dependent. However, though hypoglycemia returned to normal level after the end of the chemotherapy cycle, hyperglycemia persisted for longer duration almost till the end of observation in our study in most patients. Given the time relation between L-Asp administration and abnormal plasma glucose levels, we presume that our patients experienced L-Asp-induced hypoglycemia.

Tanaka et al. in 2012 have reported that inappropriate insulin secretion, normal free fatty acids, and low ketone bodies during severe hypoglycemia indicate hyperinsulinism, suggesting that L-Asp-induced hypoglycemia is a result of insulin hypersecretion.[9] There were no other drugs that could have potentially induced hypoglycemia during the study period.[13] There are few reports focusing on fasting glucose levels in the morning.[6,7] Glucocorticoids are known to induce hyperglycemia through insulin resistance and gluconeogenesis during induction therapy for childhood ALL.[14] We suspect that parallel use of glucocorticoids may mask the hypoglycemic effect of L-Asp. Misgar et al. in 2014 have reported a case of 15-year-old boy who developed L-Asp-induced hypoglycemia.[10]

Use of L-Asp has recently become even more common in the adult ALL regimens.[15] We believe that in addition to the effect of L-Asp on leukemic cells, it is important to pay more attention to its pharmacological features and physiological mechanisms. Greater knowledge of these effects will enable clinicians to understand and develop appropriate strategies for L-Asp use in chemotherapy regimens.

Hsu et al. in 2002 reported one case of diabetic ketoacidosis and persistent hyperglycemia as long-term complications of L-Asp-induced pancreatitis.[16] Mondal et al. in 2010 reported two cases of diabetic ketoacidosis with L-Asp therapy.[17] Quintanilla-Flores et al. in 2014 reported one case of acute pancreatitis and diabetic ketoacidosis following L-Asp/prednisone therapy in ALL.[18] Hence, to the best of our knowledge, there are only two reported cases of hypoglycemia induced by L-Asp therapy by Tanaka et al. of Tokyo, Japan, and Misgar et al. of Kashmir, India. However, in this retrospective study of ours, we have got 17 hypoglycemia as well as 13 hyperglycemia cases indicating the adverse effects of L-Asp.

Conclusions

Our study reveals that a significant percentage of cases (21%) have developed abnormal plasma glucose level among the study population. Most of them developed hypoglycemia and they were in lower age group, whereas the higher age group patients developed hyperglycemia. In comparison to peg L-Asp, native one was associated with more incidences of abnormal FPG. In majority of the cases, the FPG abnormality developed after taking three doses of L-Asp in induction phase of MCP 841 protocol. Hypoglycemia subsided whereas hyperglycemia persisted even after the stoppage of L-Asp treatment.

Identification of hypoglycemia as an adverse effect will enable clinicians to understand and develop appropriate strategies for L-Asp use in chemotherapy regimens. In addition to the effect of L-Asp on leukemic cells, it is important to pay more attention to its pharmacological features and physiological mechanisms.

Acknowledgment

I would like to sincerely thank Dr. Upendra Nayak for his support and the staff of record section for their cooperation.

Financial Support and Sponsorship

Nil.

Conflicts of Interest

There are no conflicts of interest.

References

1. Möricke A, Zimmermann M, Reiter A, Henze G, Schrauder A, Gadner H, et al. Long-term results of five consecutive
trials in childhood acute lymphoblastic leukemia performed by the ALL-BFM study group from 1981 to 2000. Leukemia 2010;24:265-84.

2. Tsuchida M, Ohara A, Manabe A, Kumagai M, Shimada H, Kikuchi A, et al. Long-term results of Tokyo Children’s Cancer Study Group trials for childhood acute lymphoblastic leukemia, 1984-1999. Leukemia 2010;24:383-96.

3. Gaynon PS, Angiolillo AL, Carroll WL, Nachman JB, Trigg ME, Sather HN, et al. Long-term results of the children’s cancer group studies for childhood acute lymphoblastic leukemia 1983-2002: A Children’s Oncology Group Report. Leukemia 2010;24:285-97.

4. Pession A, Valsecchi MG, Masera G, Kamps WA, Magyarosy E, Rizzari C, et al. Long-term results of a randomized trial on extended use of high dose L-asparaginase for standard risk childhood acute lymphoblastic leukemia. J Clin Oncol 2005;23:7161-7.

5. Raitz EA, Salzer WL. Tolerability and efficacy of L-asparaginase therapy in pediatric patients with acute lymphoblastic leukemia. J Pediatr Hematol Oncol 2010;32:554-63.

6. Pui CH, Burghen GA, Bowman WP, Aur RJ. Risk factors for hyperglycemia in children with leukemia receiving L-asparaginase and prednisone. J Pediatr 1981;99:46-50.

7. Carpentieri U, Balch MT. Hyperglycemia associated with the therapeutic use of L-asparaginase: Possible role of insulin receptors. J Pediatr 1978;93:775-8.

8. Roberson JR, Raju S, Shelso J, Pui CH, Howard SC. Diabetic ketoacidosis during therapy for pediatric acute lymphoblastic leukemia. Pediatr Blood Cancer 2008;50:1207-12.

9. Tanaka R, Osumi T, Miharu M, Ishii T, Hasegawa T, Takahashi T, et al. Hypoglycemia associated with L-asparaginase in acute lymphoblastic leukemia treatment: A case report. Exp Hematol Oncol 2012;1:8.

10. Misgar RA, Laway BA, Rahaman SH, Wani AI, Bashir MI, Bhat JR. L-asparaginase induced hypoglycemia in a case of acute lymphoblastic leukemia: A patient report. J Pediatr Endocrinol Metab 2015;28:439-41.

11. Chemotherapy in Treating Patients with Acute Lymphoblastic Leukemia and Diffuse Non-Hodgkin’s Lymphoma. Available from: http://www.clinicaltrials.gov/show/NCT00018954. [Visited on 2016 Jun 13].

12. Cryer Philip E. Glucose homestasis and hypoglycemia. In: Larsen PR, editor. Williams Textbook of Endocrinology. 10th ed. Philadelphia: W.B. Saunders; 2003. p. 1585-618.

13. Ben Saleh C, Fatallah H, Hmouda H, Bourroui K. Drug-induced hypoglycaemia: An update. Drug Saf 2011;34:21-45.

14. Lowas SR, Marks D, Malempati S. Prevalence of transient hyperglycemia during induction chemotherapy for pediatric acute lymphoblastic leukemia. Pediatr Blood Cancer 2009;52:814-8.

15. Kantarjian HM, O’Brien S, Smith TL, Cortes J, Giles FJ, Beran M, et al. Results of treatment with hyper-CVAD, a dose-intensive regimen, in adult acute lymphocytic leukemia. J Clin Oncol 2000;18:547-61.

16. Hsu YJ, Chen YC, Ho CL, Kao WY, Chao TY. Diabetic ketoacidosis and persistent hyperglycemia as long-term complications of L-asparaginase-induced pancreatitis. Zhonghua Yi Xue Za Zhi (Taipei) 2002;65:441-5.

17. Mondal R, Nandi M, Tiwari A, Chakravorti S. Diabetic ketoacidosis with L-asparaginase therapy. Indian Pediatr 2011;48:735-6.

18. Quintanilla-Flores DL, Flores-Caballero MA, Rodríguez-Gutiérrez R, Tamez-Pérez HE, González-González JG. Acute pancreatitis and diabetic ketoacidosis following L-asparaginase/prednisone therapy in acute lymphoblastic leukemia. Case Rep Oncol Med 2014;2014:139169.