

## Case Report

# Transient Diabetes Mellitus following L- Asparaginase Therapy

Ashok Shenoy Kudgi<sup>1</sup>, Mukta Nithyananda Chowta<sup>1</sup>, Rajeev Aravindakshan<sup>2</sup>

<sup>1</sup>Department of Pharmacology, <sup>2</sup>Department of Community Medicine,  
Kasturba Medical College, Mangalore, India

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## ABSTRACT

Hyperglycemia may occur as a complication in patients with leukemia during induction of remission with L-asparaginase and steroids. The reported incidence is about 10%. The presentation of this complication may vary from mild glucose intolerance to severe, or even

fatal, diabetic ketoacidosis. We report a case of a 15-year-old girl who developed transient diabetes mellitus following L-asparaginase therapy with ketoacidosis as the mode of presentation.

KEYWORDS: hyperglycemia, ketoacidosis, L-asparaginase, leukemia,

## INTRODUCTION

L-asparaginase is commonly used in combination with doxorubicin, vincristine, methotrexate and prednisolone for the treatment of acute lymphoblastic leukemia (ALL). Leukemic cells are highly sensitive to chemotherapy. In over 90% of patients, a complete remission in 4-6 weeks can be achieved with prednisolone, vincristine, L-asparaginase and doxorubicin combination chemotherapy. We report a case of severe hyperglycemia and ketoacidosis following administration of L-asparaginase in an adolescent girl.

## Case Report

A 15-year-old girl diagnosed to have acute lymphatic leukemia (FAB L1 Type) was on induction chemotherapy with vincristine, L-asparaginase, doxorubicin, intrathecal methotrexate and prednisolone as per the NCI-MCP-841 protocol<sup>[1]</sup>. The laboratory evaluation revealed hemoglobin of 45 g/l (0.70 mmol/l), total leukocyte count of  $10 \times 10^9$  cells/l and a platelet count of  $35 \times 10^9$  cells/l. Peripheral smear showed 25% leukemic blast cells. The patient received three units of packed cells prior to commencement of chemotherapy. She was given L-asparaginase at a dose of 10,000 units intravenously, vincristine 2 mg weekly, doxorubicin 40 mg weekly, prednisolone 60 mg daily and intrathecal methotrexate 12.5 mg weekly as the part of I1 regimen in the protocol. The second dose of L-asparaginase was given on day

three of induction of chemotherapy.

On day eight, patient became lethargic and irritable, developed severe abdominal pain, vomiting and deep and rapid inspiration (respiratory rate 30 / minute). Her blood pressure was 110/70 mmHg, serum amylase and electrolytes were normal. The total count was  $3.1 \times 10^9$  cells/l, hemoglobin 111 g/l (1.72 mmol/l). Suspecting septicemia, she was given ceftazidime 1 g q8H and gentamicin 100 mg q 24H. On day 10, patient did not improve and random blood sugar at this point of time was 277 mg/dl and urine tested positive for ketone bodies. There was no family history of diabetes mellitus. Regular insulin was started in a dose of four units q8H, which was escalated to 10 units q8H. The fasting blood sugar (FBS) values on days 12, 16, 18, 22 were 9.05 mmol/l, 6.77 mmol/l, 5.55 mmol/l and 3.33 mmol/l respectively. She was put on bovine insulin mixtard (30:70) in a dose of 20 units in the morning and 10 units at night on day 21 which was then reduced to 16 units morning and 8 units at night. Her blood sugar was controlled and FBS values on days 26, 29, 39 and 51 were 3.72 mmol/l, 4.61 mmol/l, 5.0 mmol/l and 3.89 mmol/l respectively. The dose of insulin was further reduced to 8 units morning and 4 units night and it was stopped on day 55. Her prednisolone dose was reduced to 40 mg/day and further to 20 mg/day over a period of five days and it was stopped on day 41. On day 38, clinical remission of ALL was obtained which was confirmed by bone marrow

Address correspondence to:

Dr. Ashok Shenoy K., Associate Professor, Department of Pharmacology, Kasturba Medical College, Light House Hill Road, Mangalore - 575001, Karnataka, India. Fax: +91-824-2425092, E-mail: ashok.shenoy@manipal.edu, dr\_ashok\_shenoy@rediffmail.com

examination. After remission, patient was taken for Regimen I2 wherein cyclophosphamide 800 mg *stat*, 6-mercaptopurine (6-MP) 75 mg daily for seven days and intrathecal methotrexate 12.5 mg weekly was administered. Cranial irradiation was given. Then the patient was subjected to consolidation chemotherapy (Regimen I2A) with 6-MP, cyclophosphamide and cytosine arabinoside.

The patient was subjected to a reinduction protocol (RI1) wherein vincristine and doxorubicin were administered as before and prednisolone at 40 mg/day. L-asparaginase was omitted. Fasting and postprandial blood sugars were monitored carefully and no elevation was found. RI1 phase was completed without any adverse event. Consolidation chemotherapy was completed on day 100. Presently, the patient has achieved remission and is on maintenance treatment with methotrexate and 6-MP.

## DISCUSSION

Several investigators have demonstrated the effect of L-asparaginase on carbohydrate metabolism. L-asparaginase has shown hyperglycemia in rabbits<sup>[2]</sup> and this has been shown to be potentiated by prednisolone<sup>[3]</sup>. Cetin M *et al*<sup>[4]</sup> have documented hyperglycemia in six out of 136 children receiving L-asparaginase wherein two developed ketoacidosis requiring insulin therapy.

Gillette *et al*<sup>[5]</sup> reported a case of transient diabetes mellitus (DM) in a 10-year-old girl who required insulin therapy. Pui *et al*<sup>[6]</sup> showed that children more than 10 years of age, a positive family history of DM and obesity had a higher risk of developing hyperglycemia. The risk and severity of DM increases when L-asparaginase and steroids are used concomitantly which is generally self-limiting<sup>[7]</sup>. However, in our case, concurrent use of steroids cannot be implicated as the sole cause since the patient did not develop hyperglycemia during the reinduction (RI2) protocol wherein prednisolone was used and L-asparaginase was omitted. In fact, in normal individuals, corticosteroids have been found to protect against fasting ketosis<sup>[8]</sup>.

The possible mechanism by which L-asparaginase causes hyperglycemia and ketoacidosis is by hypoinsulinemia resulting from an inhibition of insulin synthesis secondary to extreme depletion of L-asparagine or destruction of preformed insulin<sup>[9]</sup>. L-asparaginase can cause pancreatitis<sup>[10]</sup>. However, the clinical picture and normal serum amylase levels make pancreatitis unlikely in this patient.

We recommend that oncologists watch for this serious adverse effect even when the drug is used in low doses. Close monitoring for hyperglycemia and glycosuria should be continued during therapy.

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