

Diabetes Mellitus and Pancreatitis as a Complication of L-Asparaginase Therapy

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L-Asparaginase (L-asg) is being used over last 20 years for therapy of acute lymphoblastic leukemia (ALL)(1). The toxicities following its administration includes liver dysfunction; coagulopathy; diabetes mellitus; pancreatitis; malabsorption; severe sepsis; seizures and coma(2,3). L-asg from two different sources (*Escherichia coli* and *Erwinia caratovora*) have been studied. These two preparations are antigenically dissimilar(4) and, therefore, do not cross react with each other. However, patients treated with L-asg from *E. coli* preparation had significant higher incidence of toxicity(3).

The present communication documents development of pancreatitis and diabetes

following use of L-asg (*E. coli*). Impact on cost of therapy by use of L-asg from these two sources has been discussed, in the light of fewer side effects of *Erwinia* L-asg.

Case Report

A seven-year-old boy presented with fever, pallor and hepatosplenomegaly of one and half months duration in July 1990. He was diagnosed as a case of ALL on morphological and cytochemical characteristics. Successful induction remission was achieved with vincristine, adriamycin and L-asg (*E. coli*) and prednisolone.

The patient was in remission till April 1992, when he developed testicular and bone marrow relapse. Reinduction therapy was essentially the same as given for initial remission induction. The L-asg (*E. coli*) in dosage of 6000 units/M²/IV nine doses were given on alternate days. Pre-therapy liver function tests including transaminases, blood urea, fasting and post-prandial blood sugar, serum amylase and serum electrolytes were within normal limits. On the 5th day of L-asg therapy, the patient developed epigastric pain. Investigations showed marked hyperglycemia (fasting 295 mg/dl, post prandial 435 mg/dl), serum amylase was 490 U/L, and urine was negative for ketone bodies. He was treated with insulin and other supportive measures. Prednisolone was continued for 4 weeks but other chemotherapy was withheld because of marrow suppression. Insulin (dose varied 12-36 U/day) was given for initial 7 days while he was on steroids. Abdominal pain subsided after one week; and serum amylase returned to normal after 14 days. On follow up for last seven months his blood sugar and serum amylase levels are normal.

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Discussion

L-asg has been documented to be effective in ALL combination drug regimens(1,3,5). It acts by depletion of an aminoacid asparagin which is essential for lymphoblasts. However, this enzyme effects the synthesis of other proteins also and causes relative deficiencies of these compounds.

Hyperglycemia has been observed following administration of this drug(3). A positive family history of diabetes and obesity have been considered as risk factors(6). Risk and severity of diabetes as well as acute pancreatitis increases when L-asg and steroids are used concurrently. However, in our case L-asg appears to be causative for hyperglycemia as it was corrected without altering the steroid dosage. Hyperglycemia is generally self limiting(7) as was in our case. Hypoinsulinemia from L-asg could result from panhypoproteinaemia associated with aminoacid depletion; or as a result of toxicity the insulin release from islet cells(8) is decreased; or due to secondary hyperglucagonemia(9). It has been demonstrated that hyperglycemia secondary to hypoinsulinemia is independent of acute pancreatitis(10). However, in the present case it is not possible to determine whether hyperglycemia was secondary to acute pancreatitis, though hyperglycemia and serum amylase levels reverted to normal simultaneously.

L-asg (*E. coli*) has lower immunogenicity while Erwinia preparation has higher specific activity and low incidence of anaphylactic reactions. Although the cost of chemotherapy increases approximately by Rs. 7300/per square metre if Erwinia L-asg is used, it is observed to be safer and equally effective(3). Therefore, it may be advisable to use Erwinia L-asg as it has the

advantage of significant lower incidence of life threatening complications.

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