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TOXICITIES OF LEUNASE (L – ASPARAGINASE) ADMINISTRATION IN NORMAL HEALTHY RABBITS

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ABSTRACT

In the present study the effect of leunase (L-asparaginase) was investigated on healthy rabbits. The healthy rabbits were grouped into control and L-asparaginase treated animal. The L-asparaginase group rabbits had shown an increase in the level of serum glucose, amylase, urea and creatinine after 3 doses of 100 I.U. L-asparaginase on the 7th day of experiment, where as the level of serum protein in markedly decreased on 7th day of L-asparginase treatment. These observations suggest intervention strategies during the L-asparaginase treatment of acute lymphoblastic leukemic patients and the patients clinical monitoring for early diagnosis of these complication, is recommended.

KEYWORDS: L-asparaginase, Amylase, Glucose, Urea, Creatinine.

INTRODUCTION

Acute Lymphoblastic leukemia is the most common type of cancer in children and represents about 25% of cancers diagnosed in children.[1] L-Asparaginase has anti leukemia effects and is used for treating Acute Lymphoblastic leukemic (ALL) patients. Asparaginase catalyzes the conversion of L- Asparagine to aspartic acid and ammonia, thereby depleting serum asparagine and starving leukemic cells of the asparagine which is necessary for DNA, RNA and protein synthesis, leading to cell death.[2]

Positive outcomes of Asparaginase treatment are expected at the end of chemotherapy but some toxicities are also reported with the use of Asparaginase, which includes hypersensitivity, Pancreatitis, Thrombosis, encephalopathy, Liver disease.[3,4] and Azotemia.[5]

In the present study it was planned to assess the renal toxicities of L – Asparaginase, on normal healthy rabbits, to assess whether the toxicities produced in leukemic patients after L-asparaginase therapy is either due to the leukemic disease itself or due to L-asparaginase treatment.

MATERIAL AND METHOD

The study was conducted on normal healthy rabbits (weighting 1.02 – 1.55kg). The animals were divided into two groups namely control group and leunase (L-Asparaginase) treated group. The rabbits were treated with Leunase (L-Asparaginase) (manufactured by Kyowa Hakko Kogyoeo ltd. Tokyo, Japan) at a dose of 100 I.U intramuscularly three times in a week. The blood samples were collected on Ist day before therapy and on 7th day after 3rd dose of L-asparaginase treatment. The blood samples were drawn after 12hr fasting. The serum was analyzed for glucose, serum amylase, total protein Urea, Uric acid and Creatinine.[6] The study was approved by the ethical committee of department of Biochemistry, University of Karachi, Karachi, Pakistan.

RESULT

The weight of rabbits were taken on Ist day before the start of the experiment and on 7th day after giving three times in a week of 100 1.U of L-asparaginase intramuscularly. The samples were collected after completion of 12 hours fasting.

Table- I shows the weights of rabbits. The mean serum glucose and serum amylase levels were increased after L-asparaginase therapy as compared to before therapy, but the level of serum total protein decreased after therapy as compared to before therapy. The level of serum uric acid, creatinine and urea were also increased after L-asparaginase administration as compared to the levels before giving the drug.

DISCUSSION

In the present study we had studied the effect of Leunase (L-asparaginase) administration on normal rabbits. It was found that aspargenase which is a curative agent for

acute Lymphoblastic leukemia, has certain toxic effects on liver and kidney.

Asparaginase associated pancreatitis is the most common toxic effect.[7] In the present study an increased level of serum amylase has been found in the L-Asparaginase treated rabbits. The mechanism for development of pancreatitis is not know, the symptoms of increased serum amylase or lipase are abdominal pain, nausea and vomiting.[8]

The asparaginase treated rabbits had shown an increased level of serum glucose on 7th day of treatment. Hyperglycemia is a risk factor for developing metabolic disturbances. In the induction pahse of treatment of ALL children with L-Asparaginase in combination with corticosteroids also showed hyperglycemia.[9]

L – Asparaginase may also play a role in the pathogenesis of uretral obstruction. Azotemia is seen in a number of asparaginase treated patients.[5] In the present study serum urea, creatinine and uric acid levels were increased in L-asparaginase treated rabbits as compared to control animals. Which is in consistant to earlier findings. This may be due to the weight loss during treatment.[10]

It is concluded that administration of L-asparaginase leads to hyperglycemia, pancreatitis and an increased levels of nitrogenous compounds in blood. So it is recommended that during treatment of acute lymphoblastic leukemic patients with leunase (L-asparaginase), clinical monitoring is required for early diagnosis of hepatic & kidney disorders.

TABLE: I Body weight and serum biochemical parameters of control and L-asparaginase treated rabbits.
The body weight and serum glucose, protein, amylase, urea, creatinine and uric acid mean ±sem are tabulated. The number of animals are given in parenthesis.

Parameter	Days	Control rabbits (10)	L-Asparginase treated rabbits (10)
Weight Kg	Day 1	1.43± 0.036	1.404±0.05
	Day 7	1.49± 0.045	1.30± 0.067
Glucose mg/dl	Day 1	99.53±8.18	97.79±5.73
	Day 7	97.96±5.30	*125.44±6.87
Total Protein gm/dl	Day 1	5.60±0.16	5.74±0.28
	Day 7	5.52±0.21	*4.51±0.21
Amylase U/L	Day 1	124.36±2.29	109.59±6.85
	Day 7	125.48±3.47	*140.33±13.24
Urea mg/dl	Day 1	36.97±2.04	30.16±3.94
	Day 7	35.39±2.23	*66.12±3.63
Creatinine mg/dl	Day 1	0.86±0.05	0.88±0.09
	Day 7	1.06±0.05	*1.64±0.05
Uric acid mg/dl	Day 1	3.52±0.36	3.29±0.37
	Day 7	3.67±0.35	*5.27±0.79

*Statistically significant $P < 0.05$ as compared to Day – 1.

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