Hepatotoxicity of Chromium In Rabbits

S N I HUSAIN * S A A RIZVI ** AHMAD B * S HASAN ***

*Facultyof Pharmacy, University Of The Punjab,Lahore,Pakistan. **Pharmacist, Shaukat Khanum Memorial Hospital, Lahore.*** Physiology Dept., Allama Iqbal Medical College, Lahore.

Correspondance to: Dr Shahid Hassan

Chromium (Cr), a trace element is considered vital for many metabolic functions in the body whereas several studies have revealed that certain chromium compounds are not safe for human body. The present study was designed to see the effects of chromium citrate on SGPT, SGOT, Serum Glucose, Serum Protein and Serum Bilirubin (LFTs - Liver Function Tests) in three groups of rabbits of either sex for 21 days. Prior to drug administration the above parameters were measured in blood. Later 3, 10 and 30 mg/kg body weight of chromium citrate was given to each group of rabbits orally daily for the whole period of study. The blood samples were drawn on 0.08, 7, 14 and 21 day intervals for the measurement of above parameters.

The results exhibited that SGPT levels in rabbits did not change significantly when either of the three doses of Cr citrate were administered to the animals. However, 3 and 30 mg doses of Cr citrate decreased the levels of SGPT after 14 days of therapy. Moreover 30 mg of Cr citrate dose showed a decrease in the levels of SGPT after 21 days of therapy. No significant change was observed during the study period when SGOT levels were observed. Contrarily, 10 mg dose of Chromium citrate decreased the levels of SGOT after 0.08 and 1 day of therapy while 30 mg dose raised the SGOT after one week of therapy. With the highest dose the glucose level decreased more markedly than with the other two doses of Chromium citrate. The decreasing pattern in the serum protein levels was only observed in the initial study period (2 and 24 hours) past administration of 3 different doses of Cr citrate, after which a normalizing trend followed till the end of the study. Serum Bilirubin levels showed a constant decrease in the whole study period with the three drug doses. The data was subjected to student's t-test for statistical analysis. A more detailed study to investigate the effects on other vital organs is suggested to study the safety of Cr citrate.

Key Words: Chromium salt, liver function tests

Drug induced liver toxicity can be a potential complication of nearly every medication because liver is central to the metabolic disposition of virtually all drugs and foreign substances[1,2]. Chromium a trace element and an essential component of a balanced diet occurs in different valence states but only the trivalent and hexavalent states are commonly found[3]. Chromium is considered to be important in controlling raised glucose and lipid levels[4]. Besides therapeutic effectiveness the toxicity of chromium is already established.Trivalent Chromium is thought to have lower toxicity than hexavalent chromium[5,6]. Chromium compounds may cause allergic manifestations after exposure to either airborne particles or contact with contaminated surfaces to severe gastrointestinal and renal toxicities[7,8].The present study was undertaken to investigate effect on serum bilirubin liver enzymes, serum glucose and serum proteins after administration of three different doses of trivalent chromium citerate salt.

Materials And Methods

The study was conducted on 18 (eighteen) healthy, albino rabbits Oryctolagus cuniculus of either sex weighing 1-1.5 Kg. Three groups each comprising of six animals were housed in iron cages (3x2x2. ft) and were kept under constant environmental conditions in the animal house of the Faculty of Pharmacy, University of Punjab, Pakistan. During the acclimatization period of 4-5 days green fodder was fed to the animals whereas water was available ad libitum.

Drugs

Chromium in the form of citrates was collected from Qarshi industries Pvt.Ltd. Lahore. Hard gelatine capsules containing 3 mg, 10 mg, 30 mg chromium salt were prepared for administration to the animals. Serum glutamic pyruvic transaminase (SGPT), Serum Glutamic oxaloacetic transaminase (SGOT)[9] and serum total protein[11,12] were measured by using the kits of Randox Lab.U.K. Serum Glucose[10] was estimated by using the Biosystem Lab Kit, Spain and serum total bilirubin[13,14] was measured by the Human Lab Kit, Germany.

Study Protocol

One group was given 3mg/kg body weight of chromium citrate and the other was given 10mg/kg body weight and the last group was administered 30mg/kg body weight orally daily for 21 days. Food was withdrawn 2 hours before experimentation, however water remained available ad libitum to rabbits. Blood samples were taken from the ear marginal vein at 0.08, 1, 7, 14 and 21 days after the daily oral administration of single dose therapy. Control blood samples were taken for each parameter. Student 't'-

test was applied to determine the level of significance for each parameter.

Results

Table 1 Serum gpt(u/l) profile of rabbits that were given chromium citrate orally daily for 21 days

DAYS	Chromium citrate 3mg/kg body weight	Chromium citrate 10mg /kg body weight	Chromium citrate 30mg/kg body weight
00.00	14.67±15.0	16.33± 17	16.50±1.06
00.08	11.83± 1.17	16.83±1.08	17.50±1.61
01.00	12.17±0.95	16.67±1.25	14.67±0.72
07.00	11.33±0.15	16.50±1.65	15.83±0.79
14.00	09.83*±0.91	19.33±1.74	12.50*±0.79
21.00	15.17±2.24	16.33±1.17	13.00*±1.03

Each value is the mean ± S.E.M of 6 rabbits(n=6).P* < 0.05

Table - 1 shows SGPT levels before and after administration of chromium citrate orally daily to all the three groups of animals. Shown in the table the post dosing SGPT levels had not significantly (P>0.05) increased when compared with day zero values.

However the 3 and 30 mg/kg body weight dose of chromium citrate decreased the levels of SGPT significantly (P<0.05) after two weeks of therapy. Moreover only 30 mg/kg body weight dose of the drug displayed significant decrease (P<0.05) even after the 3rd week of therapy.

Table -II Serum got (u/l) profile of rabbits that were givenchromium citrate orally daily for 21 days

DAYS	Chromium citrate 3mg/kg body weight	Chromium citrate 10mg /kg body weight	Chromium citrate 30mg/kg body weight
00.00	11.00± 1.00	10.50±0.92	10.50±1.20
00.08	10.50 ±1.20	08.00*±0.63	10.50.92
01.00	08.50 ±1.29	07.00*±1.10	08.00±1.00
07.00	12.50 ±1.43	12.50±0.92	14.50*±1.29
14.00	08.00 ±1.29*	09.50±0.92	10.50±0.92
21.00	11.00 ±1.00	10.00±1.10	10.00±1.10

Each value is the mean ± S.E.M of rabbits(n=6).P*< 0.05

The SGOT values illustrated in table-II depict that chromium citrate at 3 mg/kg body weight had shown no significant change in the above parameter whereas 10mg/kg body weight had shown significant decrease (P<0.05) after 0.08 and 1 day of therapy. The only significant increase was observed after one week of 30mg/kg body weight chromium citrate therapy. After 21 days of therapy with all the three different doses of chromium citrate the value of SGOT corresponds nearly to the normal values.

Table III Serum glucose(mg/dl)profile of rabbits that were given chromium citrate orally daily for 21 days

DAYS	Chromium citrate 3mg/kg body weight	Chromium citrate 10mg /kg body weight	Chromium citrate 30mg/kg body weight
00.00	94.67±7.60	97.33±19.24	100.83±6.24
00.08	100.50±4.02	106.67±6.76	102.67±13.24
01.00	95.83±6.04	86.83±8.75	84.83±7.16
07.00	74.67±7.51	72.00±8.17	77.00*±8.07
14.00	65.50*±7.32	78.50±3.23	47.50***±5.58
21.00	69.83*±5.11	75.17±10.41	57.00***±7.17

Each value is the mean ±S.E.M of rabbits (n=6),p*<0.05,p** <0.01,p***<0.001

The serum glucose levels are shown in table-III which depicts a significant decrease in the parameter on the 2nd and 3rd week of therapy post administration of 3mg/kg body weight of the drug. Although 10 mg dose could not produce any significant alteration yet 30 mg did poduce significant decrease (P<0.05) in glucose levels after 1st and 3rd week of therapy.

Table IV Serum bilirubin (mg/dl) profile of rabbits that were given chromium citrate orally daily for 21 days

DAYS	Chromium citrate 3mg/kg body weight	Chromium citrate 10mg /kg body weight	Chromium citrate 30mg/kg body weight
00.00	1.10±0.06	1.06±0.05	1.09±0.08
00.08	1.01±0.06	0.97±0.03	1.02±0.01
01.00	0.92*±0.05	0.87**±0.01	0.92±0.03
07.00	0.81**±0.05	0.81**±0.05	0.90±0.08
14.00	0.85**±0.03	0.75±0.07	0.94±0.06
21.00	0.84*±0.08	0.89*±0.05	0.96±0.06

Each value is the Mean ±S.E.M (n=6).P* <0.05.P**<0.01

Table IV shows the serum protein levels to display that the 3mg/kg body weight dose significantly reduced the level of proteins in all the time intervals till first week of therapy. However the values reverted to normal at the end of the study time period. The animals treated with 10 mg dose presented significant decrease after 2 hours of therapy. However normalizing trend continued till the end of experimentation. There was a significant decrease after the 24 hours post administration of 30mg/kg body weight of the drug. Here also the values returned to the normal level till the concluding days.

Table V Serum protein (mg/dl)profile of rabbits that were given chromium citrate orally daily for 21 days

DAYS	Chromium citrate 3mg/kg body weight	Chromium citrate 10mg /kg body weight	Chromium citrate 30mg/kg body weight
00.00	6.42 ±0.17	5.89±0.14	5.66±0.38
00.08	4.69***±0.25	4.24*±0.23	5.02±0.16
01.00	4.53***±0.22	4.34**±0.20	4.54*±0.32
07.00	5.65**±0.12	5.61±0.13	5.35±0.38
14.00	6.04±0.18	5.55±0.38	5.76±0.17
21.00	6.19±0.17	5.84±0.27	5.90±0.22

Each value is the mean ± S.E.M. of 6 rabbits (n=6).p* < 0.05,p** < 0.01,p*** < 0.001

The bilirubin contents were monitored pre and post administration of three different doses of Chromium citrate as shown in table - V. The animals administered with 3 and 10 mg/kg body weight showed significant decrease from 24 hours to third week of therapy.

Discussion:

The present study elaborates the effects of different doses of chromium citrate in blood glucose levels and liver functions. It is evident from the data that SGPT levels were not raised significantly by all the doses of the drug. however a significant decrease was observed in 3 and 30 mg/kg body weight after 2 weeks of treatment. The 30 mg dose continued decreasing significantly till the third week of therapy. SGOT levels after the same dosage regimens revealed only a few significant alterations in rabbits. 10 mg/kg body weight dose produced a significant decline on the 0.08 and 1day of therapy. The dose of 30mg had induced a significant boost in SGPT levels after 7 days of

therapy. Chromium citrate doses did induce glucose lowering effects in all the groups but 3 and 30 mg doses exhibited a significant decline on 2nd and 3rd week of therapy. The serum protein profile of chromium treated rabbits showed a significant increase with all three doses of the drug. The bilirubin profile after 3 and 10 mg doses of chromium citrate displayed a significant decrease in the parameter whereas 30mg dose could not achieve significant levels.

Chromium is found to be an active ingredient for glucose tolerance factor and is reported to be essential for optimal function of insulin in mammalian tissue[15,16]. Our study has further substantiated the evidence of glucose lowering activity of chromium. Previously Afshan et al. have reported that even 1 mg/kg body weight chromium had shown significant blood glucose lowering effects in normal and diabetic rabbits[17]. The modifications were obtained in few of the serum profiles (SGPT,Glucose and Protein) at the lower and higher doses. All the three doses of chromium did produce varying degree of effects on SGOT. and bilirubin levels. Although most of the liver functions are not disturbed by the Chromium dose upto 30 mg/kg body weight yet some change could be obtained. In the present investigation The alteration brought by the lower dose of the trace element (Cr) seems to be linked with the absorption of chromium which is 0.5-1% of the administered dose. Failure to achieve a significant response at middle doses could be linked to the bell shaped dose response curve. All in all chromium citrate did not alter the LFTs to any alarming levels but these remained either within the normal values or decreased to some extent. In summary this study has shown that the different doses of chromium citrate did not elevate SGOT, SGPT, serum glucose, serum protein or serum bilirubin, rather a declining pattern in these parameter was seen. This study also reaffirms the glucose lowering effect of chromium in normal rabbits.

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