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EFFECT OF ALUMINUM CHLORIDE ON LIVER, KIDNEYAND BRAIN TISSUES IN RABBITS

(With 3 Tables and 1 Figure)

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تأثير كلوريد الألومنيوم على أنسجة كبد وكلية ومخ الأرانب

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يعد الألومنيوم أحد العناصر المنتشرة في الطبيعة بدرجة عالية حيث تصل نسبته في القشرة الأرضية حوالي ٨% مما حدا بنا إلى إجراء هذه الدراسة عن تأثير كلوريد الألومنيوم على الأرانب. استخدم في هذه الدراسة عدد ثلاثين من الأرانب النيوزيلندي البيضاء قسمت إلى مجموعتين بكل منها خمسة عشر أرنبا. تم تجريع الأرانب في المجموعة الأولى ١٠٠ ميكروجرام من كلوريد الألومنيوم لكل كيلوجرام من الوزن يوميا بواسطة اللي المعدي لمدة ستة أسابيع. تم الذبح بمعدل خمسة أرانب من كل من المجموعتين بعد أسبوعين وأربعة وستة أسابيع من المعاملة بكلوريد الألومنيوم. تم في هذا البحث دراسة التأثيرات السمية لكلوريد الألومنيوم في الأرانب على وظائف الكبد وبعض القياسات البيوكيميائية الأخرى وكذلك دراسة تركيزات الألومنيوم في اللحوم والكبد والكلى والمخ بعد أسبوعين وأربعة وستة أسابيع من إعطاء كلوريد الألومنيوم للأرانب عن طريق الفم. أظهرت النتائج زيادة تركيز الألومنيوم في مصل دم الأرانب من ٢,١٦ ميكروجرام /كيلوجرام بعد أسبوعين إلى ٥,١٨ ميكروجرام /كيلوجرام بعد ستة أسابيع من المعاملة. كانت الزيادة في تركيز الألومنيوم واضحة مع مرور الوقت فىالعضلات حيث وصلت إلي ١٦,٢٤ ميكروجرام /كيلوجرام . بلغ تركيز الألومنيوم في المخ والكبد والكلى بعد ستة أسابيع من التعرض إلي ٢٥,٢٦ و ٢٠,٣ و ٢٣,٣٦ ميكروجرام /كيلوجرام بالترتيب. مما سبق يتضح أن الكبد هو أكثر الأعضاء تركيزا للألومنيوم يليه المخ ثم العضلات ثم الكلى. أوضح البحث جليا تأثير كلوريد الألومنيوم على بعض القياسات الكيميائية الحيوية مثل البروتين الكلى واختبارات وظائف الكبد وكذلك التأثير السلبي على هضم وامتصاص المعادن الأخرى مثل النحاس والزنك والكالسيوم. يتضح من هذا البحث أن لكلوريد الألومنيوم تأثيرات سمية واضحة على وظائف الكبد وكذا الوظائف الحيوية الأخرى، كما أثبت البحث وجود الألومنيوم في أنسجة المخ والكبد والكلى بكميات كبيرة بعد التعرض لكلوريد الألومنيوم بستة أسابيع. وينصح البحث بعدم التعرض لمركبات الألومنيوم لفترات طويلة وكذلك عدم استخدام الأواني المصنوعة من أنواع رديئة من الألومنيوم في طهي الطعام واستبدالها بأوان مصنوعة من الحديد الذي لا يصدأ أو بالأواني الزجاجية.

SUMMARY

Aluminum, a neurotoxic metal, has been suggested as a possible contributing factor in Alzheimer's disease. There is a little information on the dose-related toxicity of oral Al exposure. In the current study Newzeeland white rabbits were administered aluminum chloride orally in a dose of 100 µg/Kg/day for six weeks orally. An additional group of rabbits received plain water and kept as a control group for comparison. Al concentration was measured in serum, liver, kidney, brain and muscles after two, four and six weeks of $AlCl_3$ administration. Results of this study revealed that Al concentration in the serum increased with the duration of exposure from 3.482 µg/l after two weeks to 5.330 µg/l after six weeks, while this increase with the time was clear with the duration of exposure in muscles, reaching 39.76 µg/Kg. Al concentration increases in the brain after six weeks reaching 46.87 µg/Kg. Liver and kidney showed also increase in Al concentration that reached 92.36 and 28.55 µg/Kg respectively. Effect of $AlCl_3$ on some biochemical parameters was also taken into consideration. Total protein, AST, ALT as well as G-GT showed significant difference in Al treated rabbits compared to control ones. TBARS and SOD were significantly affected with Al Cl_3 application. Estimation of some other metals showed that Cu, Zn and Ca are also involved in Al toxicity. These results indicate that Al accumulation in different tissues varies from one tissue to another.

Key words: *Aluminum concentration, Rabbit, Liver, Kidney, Brain, Muscles.*

INTRODUCTION

Aluminum (Al) is the third most abundant element (8%) in the earth's crust, exceeded by oxygen (47%) and silicon (28%). Because of its strong affinity to oxygen, aluminum never occurs as a metal in nature but is found only in the form of its compounds, such as alumina. This strong affinity to oxygen also explains why it withstood all attempts to prepare it in its elemental form until well into the 19th century. The role aluminum plays in human physiology is not known. The metal is ingested through food and water. Aluminum has been detected in the brain cells of Alzheimer's disease patients. It was demonstrated that as much as 25% of some Al salts can be absorbed from the gastrointestinal

tract (Gorsky *et al.*, 1979). Alfrey *et al.* (1979) observed that the concentration of Al in gray matter was higher in all patients that had a dialysis associated encephalopathy syndrome than in control subjects. Al toxicity has been examined in uremic patients undergoing hemodialysis. Injury to bone, liver, and erythropoietic organs has been reported in dialysis patient (Parkinson *et al.*, 1981).

Following absorption, aluminum is distributed mainly in the skeleton, liver, testes, kidneys and brain and in small amounts in other soft tissues (Venugopal and Luckey, 1978 and ATSDR, 1990). It may be involved in Alzheimer's disease (dialysis dementia) and in Amyotrophic lateral sclerosis and Parkinosism-Dementia syndromes of Guam (Guam ALS-PD complex) (ATSDR, 1990 and Goyer, 1991). Aluminum compounds can affect absorption of other elements in the gastrointestinal tract, aluminum inhibits fluoride absorption and may decrease the absorption of calcium and iron compound may possibly decrease the absorption of cholesterol by forming an aluminum pectin complex that binds fats to nondigestable vegetable fibers (Nagyvary and Bradbury, 1977). Retention of aluminum in bone is prolonged; however, it is transient in soft tissues. Renal failure increases aluminum deposition in the bone (Thurston *et al.*, 1972).

Aluminum content of seawater ranges from 3 to 2400 ppb (Venugopal and Luckey, 1978). Until recently, aluminum has existed in forms not available to human and other species. However, acid rain has increased the availability of aluminum to biological systems and has resulted in destructive effects on fish and plant species. It is unknown if humans are susceptible to this increased bioavailability (Goyer, 1991).

According to Nagy and Jobest (1994), the majority of the human population in the industrialized nations ingests a minimum of 30 to 50 milligrams of aluminum metal per day. Most foods contain aluminum products. Beverage cans, aluminum foil in contact with food, and aluminum pots and pans and aluminum in drugs including most antacids insure that the cumulative load of aluminum in the human body eventually reaches critical level.

Aluminum as consumer drugs is a big problem. Aspirin is commonly buffered with aluminum hydroxide, Aluminum glycinate and other aluminum compounds. Vaginal douches contain potassium aluminum sulfate and alum. Antacids contain aluminum hydroxide, magaldrate, dihydroxy aluminum, and aluminum oxide. Antidiarrheal drugs contain aluminum magnesium silicate and kaolin and aluminum

salt. Cake mixes, selfrising flour, processed cheese, and baking powder, food starch modifiers, pickling salts and anticaking agents provide additional aluminum in the form of sodium aluminum sulfate. It contaminates drinking water, milk and other product. It is used as a structural material in the construction, automotive and aircraft industries, in the production of metal alloys and in the electrical industry in power lines, insulated cables and wiring. Others uses of aluminum metal include cooking utensils, decorations, fencing, highway signs, cans, food packaging, foil, and dental crowns and dentures (ATSDR, 1990).

The most common food with substantial amounts of aluminum-containing additives include some processed cheese backing powders, cake mixes, frozen doughs, pancake mixes, sell-raising flours and pickled vegetables (Lione, 1983). According to Requera *et al.* (1986) and Inoue *et al.* (1988), 20% of the daily intake of the aluminum comes from aluminum cooking utensils such as pens, pots, kettles and Trayes. It has been reported that at least 303 mg of aluminum, including 206 mg revealed from an aluminum pan, are ingested in one meal of chineese noodles (Inoue *et al.*, 1988).

Concerning sources of human exposure, ingestion of aluminum present in food is identified as the main source for the general population, as food and beverages accounting for 90-95% of total daily intake. Much higher exposures are noted to occur in certain occupations and in people taking antacids and buffered analgesics. Also aluminum powder is used in paints and fireworks and natural aluminum minerals are used in water purification, sugar refining and in the brewing and paper industries. Aluminum borate is also used in the production of glass and ceramics. Al itself does not undergo metabolism in that it is absorbed and excreted unchanged. However, it is found attached to other chemicals and those moieties can change within the body. The aluminum ion is easily bound to many substances and structures in the organism, and its fate is determined by its affinity to each of the ligands and their metabolism (ATSDR, 1990). Aluminum was first recognized as the cause of low turnover osteomalacic bone disease and encephalopathy in uremic patients about a quarter century ago (ATSDR, 1990).

Sedman *et al.* (1985) published the first report of aluminum loading in the serum, urine and bones of preterm infants supported of three weeks on total parenteral nutrition (TPN). Also, the other target organs of Al is reproductive system, which decreased spermatozoa

counts and sperm motility and testicular histological and histochemical changes (Dixon *et al.*. 1979). Also, Yoshihito *et al.* (1984) observed high amount of AST, ALT, LDH, γ-GT and ALP besides necrosis of proximal tubular cells of the kidney and some regeneration was noted at day 8 from treated of aluminum nitroacetate to rats. Several investigations proved that oxidative stress has been implicated over several diseases either in humans or animals ranging from rheumatic arthritis and Hemorrhagic shock to AIDS (Osterode *et al.*, 1996).

Free radical scavenging enzymes seems to be quite important for protection against these complications and any certain biochemical changes in the cells are associated with glutathione (GSH), γ-GT and LPO. Murray (1991) said that the glutathione in liver and blood is used as indicator for the oxidative toxicants in the organs. A number of potential toxic electrophilic xenobiotics are conjugated by the nucleophilic GSH, which is an important defense mechanism against certain compounds such as some drugs or any toxic metal.

The aim of the present work was to study some toxic effects of aluminum chloride on liver, kidney, brain, muscles, and its relation to some other elements as copper, zinc, and calcium. Concentration of Al in these organs after six weeks of $AlCl_3$ adminstration was also our goal.

MATERIALS and METHODS

Thirty New-Zeeland white rabbits of body weight ranging from 1.3 to 1.6 Kg were used. Rabbits were bred and housed in cages and commercial balanced diet and water were provided during the experiment. Rabbits were divided into two groups 15 rabbits in each. The first group was given aluminum chloride orally at a dose of 100 µg/Kg daily for six weeks using a stomach tube. The second group was used as a control receiving plain water and food *ad libitum*. Aluminum chloride was used as a powder (Merck, Germany), it was dissolved in water at a concentration of 100 µg/5ml water.

Two blood samples from each animal were collected every other week from the beginning of treatment; the first in a heparinized test tubes for blood analysis while the second without anticoagulant for the serum collection. The animals were weighed every week during the experimental period which lasted 6 weeks. Immediately after sacrifice, tissue specimens were collected from liver, kidney, brain, and muscles. Tissue levels of Al was estimated in serum, liver, kidney, brain and

muscels after 2, 4 and 6 weeks chemically by Perkin Elmer 2380 Atomic Absorption Spectrophotometer according to Gajan and Larry (1972) and Nagwa *et al*. (1994).

The blood samples from all groups were collected from the heart and centrifuged at 500 rpm for 10 minuets for separation of serum. Serum total protein level was measured according to Lowery *et al.* (1951). Glutamate oxaloacetate transaminase (AST) and Glutamate pyruvate transaminase (ALT) activities were determined according to the colorimetric method of Reitman and Frankel (1957). The activity of Ɣ- glutamyl transferase (GGt) (Szasz, 1969), alkaline phosphate (Bowers and McComb, 1966). Lipid peroxide levels were measured in plasma hemolysate and tissue homogenates as thiobarbituric acid reactivity (TBARS) as described by Thayer (1984). Levels of total glutathione were measured according to Beutler *et al.* (1963). In addition, superoxide dismutase (SOD) was assayed by the method of Misra and Fridovich (1972).

RESULTS

The results of this study are presented in Tables 1, 2 and 3 and illustrated in Fig. 1.

DISCUSSION

Aluminum is released to the environment both by natural processes and from anthropogenic sources. This work was planned to evaluate the effects of orally applied aluminum chloride on rabbit. The concentrations of Al in serum, liver, kidney, brain and muscles after exposure to $AlCl_3$ (100 µg/Kg) daily for six weeks are shown in Table 1. Our results showed that the Al levels were higher than those of control rabbits indicating aluminum toxicity in rabbits associated with hepatocellular degenerative charges in liver. Venugopal and Luckey (1978) Said that aluminum is distributed mainly after absorption in the skeleton, liver, testes, kidney, brain and small amounts in other soft tissues.

Aluminum may be involved in Alzheimer's disease (Goyer, 1991). According to Kerr *et al.* (1999), Alzheimer`s disease (AD) affects the central nervous system and is the most common cause of age-related intellectual decline. The current lack of effective treatments for AD is partly due to poor understanding of its etiology, although this appears to be multifactorial. Considerable effort has been directed towards

elucidating a possible role for Al in AD. It is more likely that Al accumulates in the brain as a result of more fundamental causes and may facilitate the neurological changes, which characterize the manifestation of AD. Al is also known to be implicated in a range of other neurological diseases including atypical motor disease, Down's Syndrome, parkinsonism dementia and amyotrophic lateral sclerosis complex of Guam and the Kii peninsula of Japan. Also increasing of Al in kidney tissue causes increasing the creatinine levels indicating renal failure (Yoshihito *et al.*, 1984). Aluminum Compounds can affect absorption of other elements in the gastrointestinal tract, Al inhibits fluoride absorption and may decrease the absorption of calcium and iron Compounds (Navgyvary and Bradbury, 1977). According to present-day knowledge, Al does not rank among the essential elements. In the Al industry as well as in environmental pollution by Al, the toxic effects of Al is well known. Anyway, our results caution us against the present extensive distribution and use of Al cooking utensils.

Our results in Table 2 showed that the total protein was higher after 2, 4 and 6 weeks of administration than those in control groups. Following absorption, aluminum is distributed mainly in the skeleton, liver, testes, kidneys, and brain and in smaller amounts in other salt tissues (Venugopal and Luckey, 1978). Aluminum is not a heavy metal but it can be very toxic in excessive amounts and even smaller too if it goes to the brain. In Tables 2 and 4, results showed that the LPO, SOD and GST were significantly higher in treated rabbits in brain organ than control groups. Many of symptoms of aluminum toxicity equal to those of Alzheimer's disease, Osteoporosis and Amyotrophic Lateral Sclerosis and Parkinsonism Dementia syndromes of Guam (ATSDR, 1990 and Goyer, 1991). Serum AST, ALT, ALP, γ-GT and TBARS Concentration were significantly higher than those of the control rabbits. The differences were remarkable after 2, 4 and 6 weeks as the results of Table 3. In the study of Abd El-Nasser *et al.* (1994) have included the histopathological as well as the biochemical evaluation of aluminum-induced toxicity in rabbits. Yoshihito *et al.* (1984) observed that there is a morphological damage of the liver and kidney after treatment of aluminum for 8 day. Zinc is considered as cofactor of many enzymes as lactate dehydrogenase, alkaline phosphatase and carbonic anhydrase (Murray, 1991). The concentration of Zn in treated rabbits with aluminum shows that Zn levels were also lower than those of control

indicating also the hypogonadism (Martin, 1983). Its absorption is closely related to copper was also reported (Nagwa *et al.* 1993).

In humans, aluminum and its compounds appear to be poorly absorbed, although the rate and extent of absorption have not been adequately studied and the mechanism of gastrointestinal absorption has not yet been fully elucidated. Variability results from the chemical properties of the element and the formation of various chemical species, which is dependent upon the pH, ionic strength, presence of competing elements and presence of complexing agents within the gastrointestinal tract. The urine is the most route of aluminum excretion (WHO, 1996 and 1997). Aluminum once absorbed, is distributed in most organs within the body, it passes the blood brain barrier and is also distributed to the fetus (WHO, 1997).

As shown in Table 3, there was a highly significant increase in the value of LPO in 2, 4 and 6 weeks in liver tissue, kidney and brain in treated rabbits comparing to control groups. Also SOD behaves similar to glutathione peroxidase in liver, kidney and brain. These increasing the free radicals in the cells and gradually damage the cells. The present study showed that, aluminum cause complications in liver, kidney, muscles, brain and also affected the metabolism of some trace elements as Zn, Cu and Ca. These elements are very important for biological system in the body through the significant changes of the last parameters concerned with defense against oxidative stress either the free radical scavenging enzymes or natural antioxidants. It must be avoided, the exposure to aluminum as one of environmental pollutants that may promote production of free radicals in the body. This work also highlighted the health risks of using aluminum compounds (alum) in the purification of public water supplies.

CONCLUSION

From the above data it is noticed that, aluminum has an adverse effects on lipid peroxidation and increased free radicals inside the cells. It also affects the brain because it is a widely recognized nerve toxin. Liver and kidney functions were also affected. Al has an observable effect on the absorption of other metals as copper, zinc, and calcium. There are several recommendations that can be used to avoid antiperspirants. Nearly all antiperspirants have aluminum salts, which

are absorbed into the body. Avoid aluminum containing antacids and also avoid using food in aluminum cans.

The cans have a protective food liner, but this liner can deteriorate over time and allow aluminum from the can to seep into the food. It would also be wise to avoid soda in cans. Must be try to use the glass bottle containers if at all possible. And also avoid cooking in aluminum cookware and any cookware that is coated with a non-stick finish that is cracked. Stainless steel and glass is better.

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Table 1: Concentration of Al (µ/l) in serum, (µg/gg) liver, kidney, brain and muscles in control and treated rabbits after exposure to $AlCl_3$ (100 µg/kg body weight).

Time after exposure to $AlCl_3$ (weeks)	Parameter	Control	Treated
Two (T_1)	Serum (S)	0.22 ± 0.007	2.16±0.05 *
	Liver (L)	8.24 ± 0.05	15.52 ± 0.24*
	Kidney (K)	1.82 ± 0.018	17.14 ± 0.05 *
	Brain (B)	6.32 ± 0.08	15.2 ± 0.07*
	Muscles(M)	3.18 ± 0.05	7.62 ± 0.05 *
Four (T_2)	S	0.236 ± 0.017	2.42± 0.12 *
	L	6.2 ± 0.07	18.2± 0.07*A
	K	1.82 ± 0.008	19.46 ± 0.14*A
	B	6.22 ± 0.05	20.32 ± 0.06*A
	M	3.18 ± 0.06	12.38 ± 0.037*A
Six (T_3)	S	0.222 ± 0.006	5.18 ± 0.037*A
	L	8.38± 0.08	20.3 ± 0.03*A
	K	1.81 ± 0.08	23.36 ± 0.07*A
	B	6.38 ± 0.09	25.26 ± 0.05*A
	M	3.18 ±0.05	16.24± 0.08*A

Values are expressed as mean of 5 rabbits ± S. E. * = significant ($P < 0.05$)
P Value For Comparing Control and treated rabbits using T. test.
F test between two weeks and four weeks A = significant

Table 2: Effect of $AlCl_3$ (100 µKg B.W) on some liver function parameters in sera of rabbits after 2, 4and 6 weeks of treatments.

Parameters	Two weeks		Four weeks		Six weeks	
	C	T1	C	T2	C	T3
Total Protein (mg/ml)	45.62±0.007	40.27±0.013**	40.24±0.068	32.59±0.011**A	42.85±0.035	34.9±0.23**N.S
AST (U/ml)	9.4±0.016	12.5±0.032**	7.51±0.004	9.48±0.01**B	7.61±0.128	10.33±0.16**A
ALT (U /ml)	27.44±0.087	30.26±0.075**	27.24±0.081	35.6±0.38**B	27.23±0.156	35.66±0.30**N.S
AlKaline phosphatase (U/l)	26.04±0.15	29.01±0.063**	26.1±0.14	29.0±0.07**B	25.42±0.038	39.66±0.293**A
TBARs (nmol/ml)	0.63±0.003	2.65±0.054**	0.62±0.007	0.72±0.58**C	0.286±0.007	2.32±0.008**A
SOD (ng/ml)	12.67±0.019	29.2±0.07**	13.16±0.075	29.02±0.14**C	12.79±0.012	29.4±0.127**C
G-GT (γ-GT) (U/ml)	20.29±0.006	30.39±0.009**	21.3±0.008	34.89±0.17**B	19.89±0.198	29.42±0.236**B
Cu (µg/gm)	0.042±0.0005	0.04210.0004**	0.041±0.0004	0.036±0.0007*A	0.041±0.004	0.038±0.0005*A
Zn (µg/gm)	0.24±0.007	0.16±0.004**	0.24±0.005	0.049±0.0005**B	0.26±0.01	0.038±0.0007**B
Ca (µg/gm)	97.7±0.024	93±0.006**	97.18±0.08	80.5±0.013**B	98.6±0.043	72.7±1.3**A

Value are expressed as means of 5 rabbits ± SE

* = significant ($P < 0.05$) ** = highly significant

P = value for comparing control and treated rabbits using T-test

F test between two weeks and four weeks

A = significant B= highly significant C= N.S

Table (3) levels of lipid peroxides, Superoxide dismutase, glutathiones-s-transferase in liver, kidney, brain and tissue homogenates of untreated and $AlCl_3$-treated rabbits.

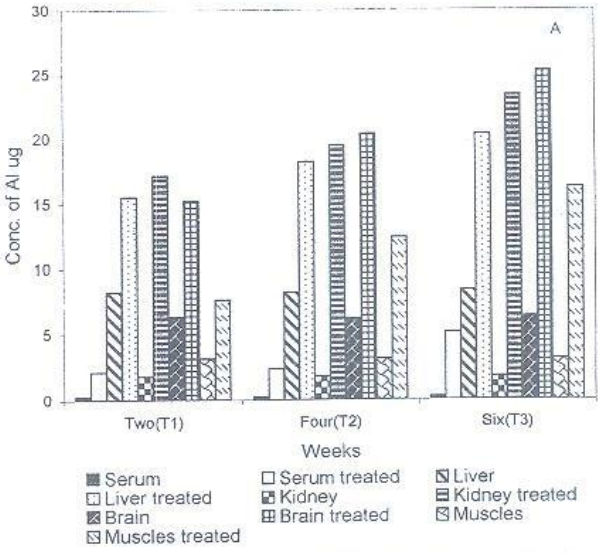
Parameter	2 weeks		4 weeks		6 weeks	
	C	T1	C	T2	C	T3
LPO (nmol/mg protein)						
Liver	0.031±0.001	0.510±0.007*	0.072±0.002	0.238±0.004*B	0.049±0.001	0.164±0.007*A
Kidney	0.129±0.002	0.544±0.005*	0.129±0.001	0.421±0.006*B	0.147±0.004	0.98±0.005*N.S
Brain	0.42±0.009	0.59±0.005**	0.37±0.007	0.80±0.006**B	0.38±0.005	0.94±0.012*B
SOD(ng/mg protein)						
Liver	3.08±0.037	4.24±0.169*	3.18±0.051	3.90±0.005*A	3.21±0.007	3.93±0.016*N.S
Kidney	2.47±0.008	4.7±0.06**	2.26±0.011	4.81±0.0**N.S	2.58±0.037	5.84±0.05 **A
Brain	4.89±0.006	8.31±0.021*	4.19±0.007	8.02±0.001**B	4.2±0.008	9.79±0.009*A
G-ST (nmol/min/ mg protein)						
Liver	500.8±0.33	516.6±1.07*	522.4±0.87	597±0.7*B	542.8±0.067	621.6±0.66*N.S
Kidney	539.8±0.58	552±0.63*	540.4±0.5	461.8±0.7*A	536.1±0.4	554.2±0.7*A
Brain	437.8±0.73	444.8±0.97*	437.4±0.5	454.4±0.8*A	433±0.14	461.2±0.8*A

Values are expressed as mean of 5 rabbit ±SE

* = Significant ** = highly significant

P = Value for comparing control and treated rabbits using T-test
F test between two weeks and four weeks

A = significant B= highly significant C= N.S


A
30
25
20
15
10
5
0
Conc. of Al ug
Two(T1)
Four(T2)
Six(T3)
Weeks
Serum
Liver treated
Brain
Muscles treated
Serum treated
Kidney
Brain treated
Liver
Kidney treated
Muscles

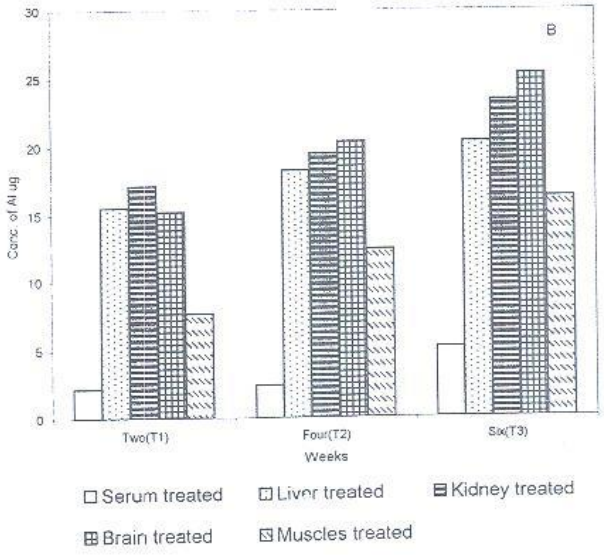

B
30
25
20
15
10
5
0
Conc. of Al ug
Two(T1)
Four(T2)
Six(T3)
Weeks
Serum treated
Liver treated
Kidney treated
Brain treated
Muscles treated

Fig. 1 (A &B)