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Original Research

Effect of aluminium administration in the rat on aluminium buildup in brain, liver and kidney

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ABSTRACT:

Aim: The present study aimed to evaluate the expression profile of both dose-dependent and time-dependent tissue accumulation of aluminiumin vital body organs including the liver, brain and kidney in three groups of male albino Wistar rats. We compared groups of rats administered with aluminium chloride and aluminium hydroxide with control-group rats to observe aluminium levels in the tissue samples.

Methods: Thirty male Wistar albino rats aged between 8-10 weeks with a body weight range of 150-205g were randomly allocated into three experimental groups of 10 animals each. Group 1 consisted of rats who received aluminium chloride ($AlCl_3$) dissolved in drinking water at dose of 0.5 mg Al/ml. Group 2 rats were orally exposed to aluminium hydroxide ($Al(OH)_3$) also dissolved in drinking water at doses of 0.5 mg Al/ml. Group 3 served as control. Aluminium accumulation in cerebral, hepatic and renal tissues was measured at specific time intervals.

Results: There was diverse daily intake of aluminium by the animals. The groups of rats treated with aluminium chloride and aluminium hydroxide had significantly higher tissue aluminium levels than those of the control group. Aluminium concentration in the kidneys of aluminium hydroxide-treated rats (range 0.14–0.86 mg/g) was generally comparable to the rats in the control group(range 0.23–0.5 mg/g). After aluminium chloride ingestion, however, significant aluminium accumulation in the kidneys was found. Cerebral aluminium concentration in the control group 1 was within the range of 0.77–3.92 mg/g. Significantly high aluminium build up in the brain was noted in group 2 (range 2.93–8.15 mg/g). In comparison, aluminium concentration in the brains of rats after aluminium hydroxide treatment was twice lower (range 1.04–8.87 mg/g) and not significantly different from control rats.Notable elevation in aluminium concentration in the liver was observed only in aluminium chloride-treated rats (range 0.1–0.5 mg/g).

Conclusion: In conclusion, the results of the current study displayed that aluminium administered orally in chloride and hydroxide forms is absorbed from the gastrointestinal tract of rats as demonstrated by tissue buildup in vital organs (brain, kidneys, liver). The extent of accumulation is contingent upon the chemical form of aluminium ingested and the type of tissue. Hence, vigilant attention is necessitated in patients requiring long-term treatment with aluminium-containing compounds as well as the possibility for buildup via dietary intake.

Keywords: Aluminium chloride, aluminium hydroxide, liver, kidney, brain dysfunction, oxidative stress

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INTRODUCTION

The environmental agent aluminium is commonly occurring and is one of the most abundant elements in the outer crust of the earth. Humans are exceedingly exposed to aluminium due to its variety of applications in the pharmaceutical and food industries. Aluminium is ubiquitous and finds its way into the environment through natural and anthropogenic sources. Taking into account the extensive uses and industrial purposes of aluminium compounds, exposure to this metal from the environment, through medicines or diet is common. Aluminium has many uses including packaging foil, and drying agents, drugs such as anticholinesterases and antiperspirants and other industrial products such as roof sheets and vehicle parts. Perhaps the numerous applications of aluminium are because of its lightweight, corrosion-free, and relative inexpensiveness. Aluminium is also noted to generate more stable compounds in biological systems as compared to magnesium or calcium. While the biochemical basis of aluminium toxicity is not entirely understood, this element amalgamates with several different compounds, significant due to their biological functions, such as ATP, GTP, DNA, RNA, proteins (transferrin, chromatin, proteins G, calmodulin, enzymes), phosphates, fluorides, and others; subsequently affecting their biological functions. Aluminium disturbs the prooxidant/antioxidant balance in tissues resulting in biochemical and physiological dysfunctions due to extreme reactive oxygen species (ROS) production. [1-6]

Dysfunction of the nervous, renal, hepatic skeletal and hematopoietic systems is caused by aluminium. It has been observed that aluminium concentration in the grey matter of patients with dialysis-associated encephalopathy syndrome was significantly higher than in control subjects.[7] Also, patients treated with dialysis after renal insufficiency were reported to suffer from dialysis encephalopathy, dialysis osteomalacia and microcytic anaemia. Explanations of mechanisms of absorption of aluminium from orally administered drugs may also be verified from reports of the same symptoms that were noted in patients treated with aluminium–containing drugs instead of dialysis. Although the gastrointestinal tract is usually an effective barrier against

aluminium absorption, however, some of it is still absorbed in the small intestine and the stomach and duodenum due to favourable pH, where the defensive role of the intestinal barrier is not as efficient. Several factors determine aluminium intestinal absorption rates, such as the presence of organic acids (citric, ascorbic) in the digestive tract, aluminium compound solubility, renal insufficiency, chemical deficiencies in diet, for example, iron and calcium, severe systemic diseases, and others.[8-10]

Although only a trivial amount of aluminium is present in food, resulting in a daily intake of 4–5 mg, and the aluminium content of drinking water is usually very low, and therefore the absorption in the gastrointestinal tract is also projected to be very low; however, with the use of aluminium-based medications, such as aluminium-containing antacids or phosphate binders, reports of aluminium accumulation in the tissues of patients are common. These reports are even more clinically relevant in dialysis patients who take medicines containing aluminium compounds. [11-14]Aluminium is an identified component of both dialysis solutions and total parenteral solutions, including calcium and phosphate salts, casein hydrolysate,heparin, and albumin. [15-20]

This results in a number of biochemical disturbances and continuing degeneration of neurones, microcytic anaemia, encephalopathy, bone fragility, andlow-turnover vitamin D-resistant osteomalacia. [21]

Despite the known toxicity of aluminium, there was little alarm about the dose and time-dependent effects of aluminium ingestion until recently, primarily due to the fact that it was presumed that aluminium was not orally bioavailable. In this study, we investigate the resultant aluminium accumulation as pertains to dose and time-dependent aluminium administration in experimental albino Wistar rats. This study operates as a touchstone to examine the rate of aluminium build-up in body tissues with respect to the rate of aluminium excretion from the body.

METHODS

Thirtymale Wistar albino rats aged between 8-10 were randomly allocated into three experimental groups of 10 animals each. The experimental first and second groups of animals were given aluminiumhydroxide andaluminium chloride, respectively, dissolved in drinking water at doses of 0.5 mg Al/ ml.The control group animals received tap water ad libitum. The diet was analysed to contain average amounts of aluminium - 68 mg/g in food and 14 ng/ml in tap water. Fluid, food consumption and body weight were recorded once a week. The experiment lasted until the total aluminium dose received by each animal in the experimental group of rats reached the value of 500 mg. The rats were put down by cervical dislocation under anaesthesia after blood with drawal. Tissue samples (liver, brain, kidneys) from experimental and control rats were excised, weighed and stored in aluminium-free plastic containers for examination of aluminium levels.

The rats were housed randomly, with equal daily periods of light and dark; in three separate metabolic rat pens of ten each, and familiarized for a week. The three groups were categorized as 1, 2 and 3. The animals in Group 1(control) were administered 0.2ml of normal saline, and the animals in groups 2and3 were administered 41 mg/kg bodyweight daily of the aluminium as in aluminium chloride and aluminium hydroxide respectively. All experimental animals were maintained on standard laboratory rat chow and water ad libitum. Each experiment was repeated and the resultant data was assembled.

Serum was collected by carotid artery cannulation from each group on days 7 and 14 employing the use of a capillary tube and transferred into plastic test tubes. Aluminium was analyzed in serum, by flameless atomic absorption spectroscopy. The organs, including, the kidneys, the liver and the brain were excised, washed with normal saline, weighed and digested. Specimens were fixed in

a mixture of 2% paraformaldehyde and 5% glutaraldehyde incacodylate buffer, washed in phosphate buffer, and fixed in 1% osmium tetroxide. The aluminium concentrations of the samples (in μg/l) were determined.

RESULTS

Table 1: Al concentrations in cerebral tissue (mg/g wet weight), exposed orally to 500 mg Al in long-term treatment

	Aluminium
Al(OH)3	2.97±2.0
AlCl3	5.50±1.61
Control group	1.54±0.67

The time needed for consumption of 500 mg Al resulted from varied daily intake (rats of the control group drank 8.9 ml water, and rats of the treated groups accordingly drank water dissolved with aluminium hydroxide of 8.6 ml and aluminium chloride of 5.9 ml. Cerebral aluminium concentration in the control group1 was within the range of 0.77–3.92 mg/g. Significantly high aluminium build up in the brain was noted in group2 (range 2.93–8.15 mg/g). In comparison, aluminium concentration in the brains of rats after aluminium hydroxide treatment was twice lower (range 1.04–8.87 mg/g) and not significantly different from control rats.

Table 2: Al concentrations in renal tissue (mg/g wet weight), exposed orally to 500 mg Al in long-term treatment

	Aluminium
Al(OH)3	0.40±0.31
AlCl3	0.36±0.14
Control group	0.18±0.09

Aluminium concentration in the kidneys of aluminium hydroxide-treated rats (range 0.14–0.86 mg/g) was generally comparable to the rats in the control group(range 0.23–0.5 mg/g). After aluminium chloride ingestion, however, significant aluminium accumulation in the kidneys was found (range 0.14– 0.68, in comparison to the range 0.05–0.32 mg/g of the rats in the control group).

Table 3: Al concentrations in hepatic tissue (mg/g wet weight), exposed orally to 500 mg Al in long-term treatment

	Aluminium
Al(OH)3	0.20±0.09
AlCl3	0.26±0.11
Control group	0.07±0.02

Notable elevation in aluminium concentration in the liver was observed only in aluminium chloride-treated rats (range 0.1–0.5 mg/g) when compared to the animals in the control group (range 0.02–0.09 mg/g).

DISCUSSION

Aluminium absorption in the digestive tract via food and medications is one of many systemic routes of exposure in humans. A number of experimental researches have been conducted to understand the impact of dose and time-dependent aluminium administration as a cornerstone of aluminium intoxication. Several techniques may be used to determine aluminium levels in biological fluids, such as graphite furnace atomic emission spectroscopy, graphite furnace atomic absorption spectroscopy, neutron activation, inductively coupled atomic emission spectroscopy, and spectrofluorimetry.[22-27]In the present study, an attempt was made to outline aluminium accumulation inthe brain, liver and kidney tissues in ratsas potentials of dose and time-dependent aluminium administered as hydroxide and chloride. The bioavailability of aluminium in the digestive tract is notably reliant on thechemical form of aluminiumingested. The results showed that oral administration of aluminium has a substantial effect on varying the amounts of aluminium contents of various tissues in rats.

Aluminium concentration was noted to be significantly higher in the cerebral tissue after days 7 and 14 respectively in Groups 1 and 2 rats treated with aluminium hydroxide and aluminium chloride when compared to those of the control group test animals. Cerebral aluminium metabolism is of particular significance since aluminium is especially neurotoxic. The brain is exceptionally susceptible to oxidative damage because of its excessive consumption of oxygen and comparatively reduced levels ofantioxidants.[28]Theseconclusions support the findings of Julka and Gill (1996) on the neurochemical effects of aluminium.[29] The authors reported an inhibitory effect of aluminium on cholinergic functioning and synaptic uptake of dopamine, norepinephrine and 5-hydroxytryptamine along with hexokinase activities and Na-K ATPase. Therefore, spontaneous nervous discharge is inhibited by aluminium, thus decreasing nervous activity. These neurological sequelae of aluminium build-up are associated with the bioavailability of aluminium in cerebral tissues through aluminium toxicity. Other neurological conditions including Alzheimer's. dementia, Parkinsonism and amyotrophic lateral sclerosis have also been linked to aluminiumbuildup.[30]

Alzheimer's disease is also an example of a condition that affects aluminium absorption, along with Down's syndrome. Subjects with Alzheimer's disease have elevated levels of aluminium absorption compared to normal. [31] A neuropathology similar to the senile dementia of Alzheimer's

The disease is noted to develop in patients with Down's syndrome. A 4 to 6-foldincrease in aluminium absorption was seen in patients with Down's syndrome compared with healthy control subjects of the same age range.[32]Tissue buildup of aluminium is also reported to be genetically conditioned.[33,34]

Our experimental model revealed the highest elevation of aluminium deposition in the tissues tested after exposure to aluminium chloride, as compared to those treated with aluminium hydroxide where lower values were detected after the administration, with osseous tissue being an exception. A lesser rise was noted in skeletal tissue (1.7 times) and renal tissue (twice). In rats who were administrated aluminium hydroxide, the aluminium buildup in the cerebral tissue doubled and was noted to be 1.6 times in the hepatic tissue, while only a minor elevation was observed in bone tissue (statistically insignificant).

It is necessary to conduct further experimental studies to assess aluminium distribution in other tissues and the potential influence of aluminium build-up on mineral metabolism.

CONCLUSION

In conclusion, the cerebral, hepatic and renal tissue aluminium levels in rats that were treated with aluminium were significantly higher than those of rats in the control group. The results of the current study displayed that aluminium administered orally in chloride and hydroxide forms is absorbed from the gastrointestinal tract of rats as demonstrated by the tissue buildup in vital organs (brain, kidneys, liver). The extent of accumulation is contingent upon the chemical form of aluminium ingested and the type of tissue. Hence, vigilant attention is necessitated in patients requiring long-term treatment with aluminium-containing compounds as well as the possibility for buildup via dietary intake.

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