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# Lethality, accumulation and toxicokinetics of aluminum in some tissues of male albino rats

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## Abstract

In the present work, the lethality percentiles including median lethal doses ($LD_{50}$), accumulation, distribution and toxicokinetics of aluminum in the liver, kidney, intestine, brain and serum of male albino rats, following a single oral administration were studied throughout 1, 3, 7, 14 and 28 days. The estimated $LD_{50}$ at 24 h was 3.45 g Al/kg body weight (b.wt.). The utilized dose of Al was 1/50 $LD_{50}$ (0.07 g Al/kg b.wt.). Aluminum residues, in Al-treated rats, were significantly decreased in response to the experimental periods and were negatively correlated with time. In addition, the hepatic, renal, intestinal, brain and serum Al contents were significantly higher than the corresponding controls at all experimental periods, except the brain that showed significant depletion when compared with its corresponding control after 28 days. Kinetically, the highest average of Al area under concentration − time curves ($AUC_{total}$, μg/g day) and area under moment concentration − time curves ($AUMC_{total}$, μg/g $day^2$) recorded in the brain followed by kidney, serum, intestine and liver. The longest elimination half-life time ($t_{1/2}$, day) and the mean residence time (MRT, day) were recorded in the brain followed by the liver, kidney, serum and intestine. On the other hand, the slowest clearance rates (Cls, L/day) of Al, in order, were recorded in brain, kidney, serum, intestine and the liver. The elimination rate constant (*Lz*, $day^{-1}$) of Al from the brain was less than that in the intestine and serum was less than that in the liver and kidney. The computed maximum concentrations ($C_{max}$) of Al in the intestine > kidney > serum > brain > liver were recorded after 3, 3.8, 2.2, 5.4 and 3.8 days, respectively. The computed starting concentration ($C_0$, μg) of Al in serum was higher than its level in the intestine followed by the brain, kidney and liver.

## Keywords

Lethality percentiles, accumulation, toxicokinetics, aluminum, rats, elimination half-life time, total clearance, mean residence time

## Introduction

Aluminum (Al) is one of the most abundant metals in the earth's crust. Human exposure to Al has been increasing over the last decades. This element appears mainly in food products and in drinking water derived from both natural sources and treatment methods (Gura, 2010). Ingestion of food, water and Al containing pharmaceuticals is the primary route of Al exposure in most humans (Gómez et al., 2008; Wang et al., 2010).

Yet, the kinetics of immediate Al disposition ingestion is poorly understood. Although serum Al concentrations are not good indicators of body Al status and toxicity as compared to Al concentrations in tissues and other fluids (Greger and Powers, 1992), most investigators have evaluated few kinetic parameters of Al only in serum or plasma following oral dosing (Wilhelm et al., 1992). Al is accepted as toxic to the central nervous, skeletal and hematopoietic systems (Poirier et al., 2011). It is known that Al may cause or contribute to specific diseases such as encephalopathy and Alzheimer's disease (Walton, 2009). The accumulation of Al likely leads to interference with

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**Table 1.** The computed lethality percentile doses of Al (g/kg b.wt.) after 24 h of oral administration.

| Lethality % | Dose | Lethality % | Dose | Lethality % | Dose |
|---|---|---|---|---|---|
| 1% ($LD_1$) | 0.20 | 30% | 1.81 | 75% ($LD_{75}$) | 7.89 |
| 5% | 0.46 | 40% | 2.53 | 80% | 9.69 |
| 10% | 0.72 | 50% ($LD_{50}$) | 3.45 | 90% | 16.63 |
| 20% | 1.23 | 60% | 4.71 | 95% | 25.97 |
| 25% ($LD_{25}$) | 1.50 | 70% | 6.57 | 99% ($LD_{99}$) | 59.94 |

important biochemical pathways by affecting the activities of some critical enzymes (Newairy et al., 2009). Jouhanneau et al. (1993) measured the concentrations of $^{26}Al$ in plasma, liver and bone of rats 8, 24 and 48 h after its ingestion with and without citrate. Quartley et al. (1993) sampled a variety of tissues in rats 2, 4, or 24 h after they received a single oral dose of aluminum citrate. These investigations probably missed tissue Al uptake and elimination that occurred immediately following absorption. The full toxicokinetic parameters of Al are not well studied and need great attention to discuss the toxicity of this metal to mammals.

The goal of the present work is to study the lethality percentiles, accumulation and full toxicokinetics ($AUC_{total}$, $AUMC_{total}$, mean residence time (MRT), $t_{1/2}$, Cl, $C_{max}$, $T_{max}$ and $C_0$) of Al in the liver, kidney, intestine, brain and serum after a single oral administration of 0.07 g Al/kg body weight (b.wt.) throughout 1, 3, 7, 14 and 28 days.

## Materials and methods

### Experimental animals

Healthy adult male albino rats (120 $\pm$ 20 g) were purchased from the animal house of National Research Center. Rats were housed in plastic cages in air-conditioned room (temperature of 22 $\pm$ 2°C). Animals were maintained on standard pellet diet and given deionized water *ad libitum*. Animals used for procedure were treated in strict accordance with the National Institutes of Health Guide for Care and Use of Laboratory Animals (1985). The present work was performed in the laboratory of Zoology Department, Faculty of Science, Cairo University, Egypt.

### Chemicals and reagents

Al as hydrate aluminum chloride ($AlCl_3{\cdot}6H_2O$) was purchased from Alpha Trade Group Company for chemicals, Cairo, Egypt. All other analytical laboratory chemicals and reagents (concentrated pure Perchloric ($HClO_4$) and nitric acid ($HNO_3$) were purchased from Sigma (Egypt).

### Estimation of aluminum lethality percentiles

Lethality percentiles of Al ($LD_1$, $LD_{50}$ and $LD_{99}$) including the median lethal dose ($LD_{50}$), following oral administration of aluminum chloride were estimated to identify the suitable dose for the present work. Rats were divided randomly into five groups each with five rats. The first to the fifth group were administered 0.5, 1.25, 2.5, 3.5 and 4 g $AlCl_3$/kg b.wt., respectively. The number of the dead rats in each group was recorded throughout 24 h of administration. Probit analysis was used to compute the lethality percentiles of Al by aid of NCSS 2007 software. The calculated $LD_{50}$ was 3.5 g/kg b.wt. (Table 1).

### Experimental design

Toxicokinetics of Al as $AlCl_3{\cdot}6H_2O$ was estimated following a single oral dose of the metal to the experimental animals by the gastric intubation technique. Experimental periods were 1, 3, 7, 14 and 28 days. Fifty health male albino rats were used in this study. Animals were randomly divided into 2 groups, each with a size of 25 rats ($n = 25$). Rats of the first group (control, group 1) were administered deionized water whereas those of the second group was administered a single dose of aluminum chloride that equal 1/50 $LD_{50}$ (3.5 g/50 = 0.07 g/kg b.wt.).

At end of the experimental period (1, 3, 7, 14 and 28 days), the blood was collected from retro-orbital plexus of rats by aid of capillary tube. The blood was decant into a centrifuge tube and then centrifuged at 3000 r/min for 20 min, then the clear supernatant yellowish serum was drawn by Pasteur pipette and kept in clean dry vials for Al analysis. After the blood collection rats were dissected quickly to obtain the desired tissues (liver, kidney, brain, and intestine) and stored at −20°C for metal analysis (Figure 1).

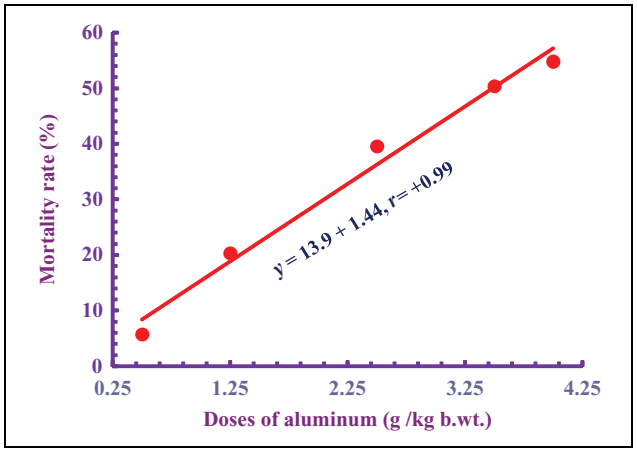


**Figure 1.** Relationship between the mortality rate (%) of male albino rats and administered oral graded doses of aluminum as $AlCl_3$.

### *Chemical analysis of aluminum*

The studied tissues were homogenized and digested with mixture of concentrated nitric acid ($HNO_3$) and perchloric acid ($HClO_3$) in 4:1, v: v, according to method described by Protasowicki (1985). After evaporation of acids (by heating block) and cooling of the samples, the ash residue on the wall and bottom of tube was dissolved in 15% $HNO_3$. Concentrations of Al were determined with inductively coupling plasma. The working standards of Al (0, 50, 100, 200, 400, 600, 800 and 1000 µg/L), aspirated and followed by the diluted tissue samples. The Al contents were determined from the calibration graph of recorder signal peak height versus Al concentrations. The tissue Al content was calculated from a relevant calibration curve. The residuals of Al in tissues were expressed as microgram per gram wet weight (µg/g wet wt.).

### *Aluminum kinetics assay*

Al toxicokinetics was computed according to Amisaki and Tatsuhara (1988). Because Al was orally administered, the extravascular noncompartmental analysis (NCA) kinetics was used to compute the kinetic parameters of Al in tissues by aid of Kinetica Software package program version 6. The estimated kinetics of Al in the tissues were total area under concentration − time curve ($AUC_{total}$), using the linear trapezoidal rule with extrapolation to infinity time; the total area under the first moment curve ($AUMC_{total}$). The mean resident time (MRT, the average time necessary to the molecules of a given dose spend in the body), the total clearance (Cl, the removal rate of the molecules per unit time) of Al from the tissues were computed.

$$AUC_{total} = \int_{t_n}^{t_x} C\mathrm{d}t = \frac{C_n}{\lambda_z}$$

$$AUMC_{total} = \frac{C_n}{\lambda_z^2} + \left(t_n \times \frac{C_n}{\lambda_z}\right)$$

$$MRT = \frac{AUC_{total}}{AUMC_{total}}$$

$$Cl = \frac{Dose}{AUC}$$

The apparent starting ($C_0$, the concentration of the metal at starting of experiment), the maximum ($C_{max}$, the maximum peak of the metal at $T_{max}$) tissue contents of Al and the corresponding starting ($T_0$, the staring time of experiment) and maximum ($T_{max}$, the time at which Al reached its maximum peak) times were calculated by analyzing the data. The terminal elimination rate constant ($Lz$) was derived from the slope of linear equation of log-transformed data for each tissue. The terminal biological half-life time of Al ($t_{1/2}$, the time necessary for Al concentration to decline by 50%) was calculated according to the following formula:

$$t_{1/2} = \frac{\ln 2}{Lz}$$

### *Statistical analysis*

Statistically, data were analyzed by aid of SPSS version 18 package software. One-way analysis of variance (ANOVA) was applied to test the effect of experimental time on Al residue in the studied tissues. In addition, Duncan's test was used to estimate the homogeneity (similarity) between the experimental studied groups of the control or the Al-administered rats. The least significant difference (LSD) was executed to compare between the studied parameters of group 2 (Al-administered rats) and group 1 (control).

## Results

The lethality percentiles of Al doses ($LD_1$, $LD_{50}$ and $LD_{99}$) at 24 h, in male albino rats, following oral administration of the metal are recorded in Table 1. The computed $LD_{50}$ was 3.45 mg Al/kg b.wt. The hepatic, renal, brain, intestinal, and serum Al contents

of controls (group 1), throughout the course of experiments, were not affected by experimental periods (time), whereas Al-administered rats (group 2) were significantly influenced (Table 2). According to Duncan's test of homogeneity, Al contents in all studied tissues of group 1 were similar at all experimental periods, that is no significant difference was recorded (Table 2). The LSDs pointed to the hepatic, renal, brain, intestinal and serum Al content in rats of group 2 were significantly increased in comparison with the corresponding control at all experimental periods except in serum where, Al concentration depleted significantly after 28 days (Table 2). On the other hand, no significant difference was recorded for Al residue in the liver and kidney of group 2 when compared with their corresponding control after 28 days postadministration with 0.07 g/kg b.wt. (Table 2).

One-way ANOVA revealed that $AUC_{total}$ and the $AUMC_{total}$, in the rats of group 2, were affected significantly by the experimental periods (Table 3). In descending order, the highest values of $AUC_{total}$ and $AUMC_{total}$ were recorded in the brain followed by kidney, serum, intestine and the liver after 28 days (Table 3). After 1 day of experiment, $AUC_{total}$ was similar (homogenous) in the renal, brain, intestinal tissues and serum but differed (no similarity) with the hepatic tissue (Table 3). In addition, at 28th day, $AUC_{total}$ in the intestine and serum was similar and significantly differed from that in the hepatic, renal and brain tissues (Table 3). On the contrary, $AUMC_{total}$ was similar in all the studied tissues after 1 day, whereas its average in the hepatic tissue was significantly less than its value in the brain and renal tissues followed by serum and the intestine (Table 3).

The kinetic parameters of Al, following a single oral administration of 0.07 g Al/kg b.wt., including the biological half-life time of elimination ($t_{1/2}$), MRT, Cl, clearance coefficient ($Lz$), initial concentration of Al at starting the experiments ($C_0$), maximum concentration of Al ($C_{max}$) at maximum time ($T_{max}$) in the hepatic, renal, intestinal, brain and serum were estimated (Tables 3 and 4). As shown in Table 3, once Al concentration peaked, the redistribution and elimination of the metal from serum and other tissues began. After 28 days postadministration with a single dose of 0.07 g/kg b.wt. of Al, the metal content in all the studied tissues dropped to values which were very closed to those of corresponding control, except the brain that was significantly higher than corresponding control (Table 3). The highest ($2.59 \pm 0.09$) and lowest ($1.37 \pm 0.09$) average of $C_{max}$ of Al were recorded in the intestinal and hepatic tissues after 3 and 3.8 days, respectively (Table 4). In rats of group 2, $t_{1/2}$ and MRT in the brain were significantly higher than in other studied tissues (Table 4) and accompanied with slowest clearance rate (Cl, $0.005 \pm 0.002$). Average values of $t_{1/2}$, MRT and Cl confirmed that the most favorite tissue for Al accumulation is the brain followed by the liver, kidney and intestine (Table 4). The lowest elimination rate constant was recorded in the brain, whereas the highest averages were recorded in intestine and serum (Table 4).

## Discussion

In order to estimate the safe dose of Al, in the present work, the lethality percentile doses of the metal including $LD_{50}$ in male albino rats at 24 h were studied. The computed $LD_{50}$ was 3.45 g Al/kg b.wt. The actual $LD_{50}$ of Al are unclear due to insufficient information on Al intake from the base diet. For the Al nitrate form, $LD_{50}$ values of 261 and 286 mg Al/kg have been reported for Sprague-Dawley rats and Swiss Webster mice, respectively (Llobet et al., 1987). For the Al chloride form, $LD_{50}$ values of 370, 222 and 770 mg Al/kg have been reported for Sprague-Dawley rats, Swiss Webster mice and male Dobra Voda mice, respectively (Llobet et al., 1987; Ondreicka et al., 1966). For Al bromide, $LD_{50}$ values of 162 and 164 mg Al/kg have been reported in Sprague-Dawley rats and Swiss Webster mice, respectively (Llobet et al., 1987). The $LD_{50}$ for aluminum sulfate in male Dobra Voda mice was reported as 980 mg Al/kg (Ondreicka et al., 1966). A single gavage exposure to 540 mg Al/kg as aluminum lactate was fatal in 5 of 5 lactating female New Zealand rabbits (Yokel and McNamara, 1985). Time to death way reported was as 8–48 h.

In the present results, we demonstrated that the gavages administration of a single dose (0.07 g Al/kg) of $AlCl_3$ caused the uptake of measurable amounts of Al in a variety of tissues in rats. Moreover, Al concentrations in tissues decreased with time; and they were inversely correlated to the length of time but still higher than their corresponding controls except in the brain at 28th day. Al and its compounds tend to solubilize into trivalent $Al^{3+}$ cations in acid environments below pH 5, a phenomenon that makes exterior Al surfaces corrodible in acid rain. In the same way, dietary Al compounds dissociate in stomach acid to become unattached legends and free Al ions that subsequently hydrate to form trivalent aluminum hexahydrate (Keith et al., 2002). Low levels

**Table 2.** Aluminum residues in the liver, kidney, brain, intestine (μg/g wet wt.) and serum (μg/ml) of control (group 1) male albino rats and those orally administered a single dose of 0.07 g Al/kg b.wt. (group 2) after 1, 3, 7, 14 and 28 days.[a]

| Tissues | Exp. groups | 1 day | 3 days | 7 days | 14 days | 28 days | Time effect (ANOVA) |
|---|---|---|---|---|---|---|---|
| Liver | Group 1 | $0.58 \pm 0.015^{b}$ | $0.59 \pm 0.004^{a}$ | $0.60 \pm 0.040^{a}$ | $0.55 \pm 0.013^{a}$ | $0.56 \pm 0.019^{a}$ | $F_{4,20} = 0.9$, $p > 0.05$ |
| | Group 2 | $0.83 \pm 0.048^{c**}$ | $1.33 \pm 0.072^{e***}$ | $1.16 \pm 0.111^{d***}$ | $0.78 \pm 0.027^{bc**}$ | $0.66 \pm 0.051^{ab}$ | $F_{4,20} = 17.04$, $p < 0.000$ |
| | % change | +43.1% | +125.42% | +93.33% | +41.82% | +17.86% | |
| Kidney | Group 1 | $1.25 \pm 0.038^{a}$ | $1.24 \pm 0.058^{a}$ | $1.20 \pm 0.021^{a}$ | $1.18 \pm 0.020^{a}$ | $1.17 \pm 0.07^{a}$ | $F_{4,20} = 1.63$, $p > 0.05$ |
| | Group 2 | $1.48 \pm 0.092^{c*}$ | $2.47 \pm 0.058^{e***}$ | $2.16 \pm 0.113^{d***}$ | $1.43 \pm 0.068^{bc*}$ | $1.30 \pm 0.073^{ab}$ | $F_{4,20} = 38.54$, $p < 0.000$ |
| | % change | +18.40% | +104.13% | +80.00% | +21.20% | +11.11% | |
| Intestine | Group 1 | $0.41 \pm 0.007^{a}$ | $0.42 \pm 0.014^{a}$ | $0.44 \pm 0.018^{a}$ | $0.45 \pm 0.047^{a}$ | $0.48 \pm 0.020^{a}$ | $F_{4,20} = 1.19$, $p > 0.05$ |
| | Group 2 | $2.07 \pm 0.089^{e***}$ | $2.59 \pm 0.096^{f***}$ | $1.88 \pm 0.040^{d***}$ | $1.17 \pm 0.053^{c***}$ | $0.87 \pm 0.021^{b***}$ | $F_{4,20} = 109.6$, $p < 0.000$ |
| | % change | +404.87% | +516.67% | +327.20% | +160% | +81.25% | |
| Brain | Group 1 | $1.39 \pm 0.055^{a}$ | $1.39 \pm 0.005^{a}$ | $1.36 \pm 0.058^{a}$ | $1.35 \pm 0.053^{a}$ | $1.33 \pm 0.007^{a}$ | $F_{4,20} = 1.03$, $p > 0.05$ |
| | Group 2 | $1.63 \pm 0.041^{de**}$ | $1.84 \pm 0.073^{f***}$ | $1.84 \pm 0.043^{f***}$ | $1.70 \pm 0.042^{cd***}$ | $1.52 \pm 0.06^{ef**}$ | $F_{4,20} = 6.95$, $p < 0.001$ |
| | % change | +17.27% | +32.37% | +35.29% | +12.68% | +32.81% | |
| Serum | Group 1 | $1.06 \pm 0.048^{a}$ | $1.04 \pm 0.005^{a}$ | $1.01 \pm 0.036^{a}$ | $0.99 \pm 0.032^{a}$ | $1.05 \pm 0.056^{a}$ | $F_{4,20} = 1.65$, $p > 0.05$ |
| | Group 2 | $2.18 \pm 0.089^{f***}$ | $1.60 \pm 0.061^{d***}$ | $1.91 \pm 0.037^{e***}$ | $1.31 \pm 0.029^{c***}$ | $0.86 \pm 0.041^{a**}$ | $F_{4,20} = 84.99$, $p < 0.000$ |
| | % change | +105.66% | +53.84% | +89.10% | +32.32% | +18.10% | |

[a]Values are represented as mean ± standard error.

In the row, values marked with the same superscript letters are similar (insignificant difference, at $p > 0.05$), whereas those marked with different superscript letters are not similar (significant difference, at $p < 0.05$). The symbols *, ** and *** indicate significant differences with the corresponding controls at confidence levels of 0.95, 0.99 and 0.999, respectively. $p > 0.05$, insignificant effect whereas $p < 0.001$ and $p < 0.000$ significant effect at confidence levels 0.99 and 0.999.

**Table 3.** The total area under curve($AUC_{tot}$, μg/g day) and total area under moment curve ($AUMC_{tot}$, μg/g $day^2$) of aluminum in the liver, kidney, brain, intestine and serum ($AUC_{tot}$, μg/ml day); ($AUMC_{tot}$, μg/ml $day^2$) of male albino rats, throughout 1, 3, 7, 14 and 28 days after a single oral administration with 0.07 g Al/kg b.wt.[a]

| | Time | Liver | Kidney | Brain | Intestine | Serum |
|---|---|---|---|---|---|---|
| $AUC_{total}$ | 1 day | $0.83 \pm 0.05^{b}$ | $1.48 \pm 0.09^{b,c}$ | $1.63 \pm 0.04^{b,c}$ | $2.07 \pm 0.09^{c}$ | $2.18 \pm 0.09^{c}$ |
| | 3 days | $2.16 \pm 0.06^{c}$ | $3.96 \pm 0.12^{d,e}$ | $3.47 \pm 0.08^{d}$ | $4.66 \pm 0.15^{e,f}$ | $3.74 \pm 0.15^{d}$ |
| | 7 days | $4.96 \pm 0.30^{f}$ | $9.24 \pm 0.25^{h}$ | $7.36 \pm 0.22^{g}$ | $8.87 \pm 0.19^{h}$ | $7.01 \pm 0.15^{g}$ |
| | 14 days | $6.69 \pm 0.28^{g}$ | $12.36 \pm 0.38^{l}$ | $12.41 \pm 0.23^{l}$ | $10.49 \pm 0.32^{i,j}$ | $11.12 \pm 0.13^{j,k}$ |
| | 28 days | $10.04 \pm 0.43^{i}$ | $19.04 \pm 0.78^{n}$ | $22.48 \pm 0.42^{o}$ | $14.18 \pm 0.36^{m}$ | $14.92 \pm 0.34^{m}$ |
| Time effect (ANOVA) | | $F_{4,20} = 187.7$, $p < 0.000$ | $F_{4,20} = 289.3$, $p < 0.000$ | $F_{4,20} = 1081.9$, $p < 0.000$ | $F_{4,20} = 384.4$, $p < 0.000$ | $F_{4,20} = 752.3$, $p < 0.000$ |
| $AUMC_{total}$ | 1 day | $0.41 \pm 0.02^{b}$ | $0.74 \pm 0.05^{b}$ | $0.81 \pm 0.02^{b}$ | $1.03 \pm 0.04^{b}$ | $1.09 \pm 0.04^{b}$ |
| | 3 days | $4.82 \pm 0.19^{b}$ | $8.90 \pm 0.21^{b}$ | $7.15 \pm 0.22^{b}$ | $9.84 \pm 0.33^{b}$ | $7.29 \pm 0.28^{b}$ |
| | 7 days | $24.70 \pm 1.65^{c}$ | $45.78 \pm 1.38^{d}$ | $36.94 \pm 1.02^{c,d}$ | $43.41 \pm 0.85^{d}$ | $36.32 \pm 0.66^{c,d}$ |
| | 14 days | $68.77 \pm 2.49^{e}$ | $126.79 \pm 3.85^{g}$ | $129.70 \pm 2.40^{g}$ | $107.27 \pm 3.44^{f}$ | $114.32 \pm 1.37^{f,g}$ |
| | 28 days | $209.17 \pm 9.81^{h}$ | $398.23 \pm 16.42^{j}$ | $468.94 \pm 9.50^{k}$ | $292.97 \pm 6.91^{i}$ | $306.07 \pm 7.62^{i}$ |
| Time effect (ANOVA) | | $F_{4,20} = 358.1$, $p < 0.000$ | $F_{4,20} = 478.0$, $p < 0.000$ | $F_{4,20} = 2638.2$, $p < 0.000$ | $F_{4,20} = 1200.6$, $p < 0.000$ | $F_{4,20} = 1341.7$, $p < 0.000$ |

[a]Data are expressed as mean ± standard error. $p < 0.000$ indicates a significant effect of time at confidence level 0.999. The values marked with the same superscript letters are similar ($p > 0.05$) while those with different superscript letters are not similar ($p < 0.05$).

**Table 4.** The maximum time ($T_{max}$, day), the elimination rate constant ($Lz$, day$^{-1}$), the elimination half-life time ($t_{1/2}$, day), mean residence time (MRT, day), total clearance (Cl, L/day), the maximum ($C_{max}$) and starting concentration ($C_0$) of aluminum in the liver, kidney, brain, intestine (μg/g wet wt.) and serum (μg/ml) of male albino rats, throughout 1, 3, 7, 14 and 28 days of a single oral administration of 0.07 g Al/kg b.wt.[a]

| Tissue | $T_{max}$ | $C_{max}$ | $C_0$ | $Lz$ | $t_{1/2}$ | MRT | Cl |
|---|---|---|---|---|---|---|---|
| Liver | 3.80 | 1.37 ± 0.09$^b$ | 0.83 ± 0.05$^b$ | 0.03 ± 0.00$^c$ | 30.71 ± 7.19$^b$ | 45.47 ± 9.92$^b$ | 1.389 ± 0.18$^d$ |
| Kidney | 3.80 | 2.48 ± 0.06$^e$ | 1.48 ± 0.09$^c$ | 0.03 ± 0.00$^c$ | 28.59 ± 4.08$^b$ | 43.33 ± 5.93$^b$ | 0.723 ± 0.07$^c$ |
| Brain | 5.40 | 1.88 ± 0.06$^c$ | 1.63 ± 0.04$^c$ | 0.01 ± 0.00$^b$ | 85.71 ± 17.40$^c$ | 124.22 ± 25.14$^c$ | 0.334 ± 0.01$^b$ |
| Intestine | 3.00 | 2.59 ± 0.09$^e$ | 2.07 ± 0.09$^d$ | 0.04 ± 0.00$^d$ | 16.54 ± 0.47$^b$ | 25.14 ± 0.74$^b$ | 1.148 ± 0.03$^d$ |
| Serum | 2.20 | 2.18 ± 0.09$^d$ | 2.18 ± 0.09$^d$ | 0.04 ± 0.00$^d$ | 19.08 ± 1.38$^b$ | 28.52 ± 2.05$^b$ | 1.121 ± 0.05$^d$ |

[a]Values marked with the same superscript letters are similar, whereas those marked with different superscript letters are significantly different.

of liberated free Al re-complexes with the original or another available legend in a manner that preferentially favors carboxylic acids (citrate or lactate). The majority (>99%) passes unattached into the duodenum where the increased alkalinity sequentially deprotonates the aluminum hexahydrate ion into insoluble aluminum hydroxide, which is primarily excreted in the feces (Keith et al., 2002). A small fraction of Al becomes systemic through processes that have not yet been elucidated but are believed to involve passive paracellular or transcellular diffusion. An additional and unique carboxylic acid-mediated mechanism enhances gastrointestinal tract absorption by more than an order of magnitude (Domingo, 1995; Greger and Donnaubauer, 1986). As heavy metals, the transport of Al into the intestinal mucosal cells probably follows the first-order kinetics but may be assisted by low-molecular-weight ligands (linear kinetic model), in particular, metalloproteins, although their presence is not obligatory for transport to take place (Reynders et al., 2008). The transport of Al from the mucosa to the blood stream is much less than for essential metals, such as zinc, where it may reach 50% (Dua et al., 2010). In an experiment, cadmium absorbed into mucosal cells, but not transferred to the blood stream, is bound to cell membranes and returns to the gastrointestinal tract following the desquamation of these cells (Ben Amara et al., 2011). Once Al is in the bloodstream, it distributes widely to the various body tissues in a pattern that may parallel the density of transferrin receptors within those tissues (Walton, 2011). Systemic Al binds to serum proteins or anions and is distributed rapidly to other tissues throughout the body. Approximately, 89% of the Al reaching the blood binds with transferrin and the rest mainly attaches to citrate. This suggestion discuss the depletion of Al content in serum and its elevation in the intestine, kidney, brain and liver that in turn reached its lowest level 28 days posttreatment with the metal.

Kinetically, several methodological problems have limited the investigation of Al in tissues where Al is ingested. The first reason is the lack of suitable isotopes (Ganrot, 1986) and the second is the difficulty to monitor loss of Al from tissues with time when only small amounts of Al are deposited initially in the tissues of animals treated with Al in feed or water (Greger and Powers, 1992). Wilhelm et al. (1990) noted that calculations of biological half-life of Al were compromised when the postdosage period was too short. Previously, follow-up periods have been 10 h (Greger et al., 1994), 50 h (Yokel and McNamara, 1988), 13 days (Burgess et al., 1992) and 21 days (Greger and Donnaubauer, 1986; Greger et al., 1994). On the other hand, other authors monitored tissue Al concentrations for 45 days (Greger and Radzanowski, 1995) and 113 days (Yokel and McNamara, 1989) after dosing. We monitored tissue Al concentrations for 28 days after dosing in this study. All previous studies were concentrated only on estimation of half-life period of Al elimination without attention to other kinetic parameters of the metal in tissues. The present study gave great attention to full kinetics of Al in the liver, kidney, intestine, brain and serum of male albino rats throughout 1, 3, 7, 14 and 28 days of ingestion with a single dose (0.07 g) of Al. The present finding confirmed that intestine is an intermediate step for absorption and transport of Al through blood-bound albumin into other tissues.

The highest average of area under concentration − time curves ($AUC_{total}$) and area under moment concentration − time curves ($AUMC_{total}$) was recorded in the brain followed by kidney, intestine and serum.

This finding indicated the high response of the brain followed by other studied tissues to the low dose of the metal (Krewski et al., 2007). Al-bound protein is released into the circulation and then filtered by kidney and reabsorbed by cells of proximal tubules. Thus Al accumulates in renal tubular cells, until the synthetic capacity for metalloprotein is exceeded, that is Al $AUC_{total}$ can be used as a mirror and determinant toxicokinetic parameter for Al accumulation and distribution not only at target tissues but at the active sites for metal binding, that is the increase in target tissue Al $AUC_{total}$ and $AUMC_{total}$ will be associated with marked increase in Al accumulated by tissues (Sánchez-Iglesias et al., 2007).

The elimination half-life time ($t_{1/2}$) and the mean residence or MRT and the Cl of Al in the studied tissues were highly approvable with the recorded $AUC_{total}$ and $AUMC_{total}$ in the corresponding tissue of rats treated with Al. Tissues (brain, liver and kidney) with high Al $AUC_{total}$ and $AUMC_{total}$ have longer $t_{1/2}$ and MRT more than other tissues, confirming their high ability to store Al in a molecular form (Krewski et al., 2007). The recorded long Al $t_{1/2}$, in the present work and MRT in the liver and kidneys confirmed that these tissues are main excretory route for Al. In addition, the brain has the longest $t_{1/2}$ and MRT and slowest clearance rate. In the present study, the retention of Al is directly affected by excretion. According to Xu et al. (1991 and 1992), 66–70% of the injected Al was excreted in 24 h. In a human study, Priest et al. (1998) injected a volunteer with 0.7 μg of radioactive $^{26}$Al as citrate and followed blood levels and body elimination. They found that more than 50% of the Al distributed from blood to other body tissues in 15 min. Long-term observation using excreta and whole body monitoring found excretion of >50% in 24 h, 85% at 13 days and 96% by 1178 days. Elimination followed a power function featuring a rapid initial release followed by successively longer-term components.

The question of Al toxicokinetics in the brain is of great interest because of the toxic effects Al has in the organ. Al can cross the blood–brain barrier (Erazi et al., 2010). Normal uptake of the metal by the brain, which is very sensitive to Al, is very slow but it cannot be eliminated from the brain and therefore accumulates (Baydar et al., 2005) to high levels inducing disorders in the brain regions (Poirier et al., 2011). This results in an overall slow buildup of Al in the body over a lifetime. The elimination half-life time of Al in the present study (Table 4) does not agree with some authors. In Al-treated rabbit, Yokel and McNamara (1989) reported that half-lives of Al were 113 days in spleen, 74 days in liver, 44 days in lung, 42 days in serum, 4.2 days in kidney cortex and 2.3 days in kidney medulla. The kidney also demonstrated another half-life greatly exceeding 100 days. The results of this study demonstrate that Al persists in various tissues and fluids for different lengths of time. The calculated half-life of Al in these tissues is substantially longer than previously estimated half-lives based on serum Al determination. On the other hand, Sutherland and Greger (1998) assessed the kinetics of Al uptake and elimination by Sprague-Dawley rats following a single gavage dose of 0, 0.25, 0.5 or 1 mmol Al/kg b.wt. in 1 ml of 16% citrate. They reported that, the elimination half-lives of Al from serum (102–119 min), liver (267–465 min) but could not be estimated in bone and kidney because of turnover exceeded the 6 h collection. Al elimination half-lives in liver, bone and kidney were generally dose independent. Disagreement for elimination half-lives of Al from tissues of experimental animals, in the present work and previous studies, may be attributed to mode of metal administration, doses and the experimental animals.

In conclusion, Al accumulation happens in certain favorite target organs such as the liver, kidney and brain. The differential aluminum kinetics in the most important organs clarified the high affinity of aluminum to penetrate the blood brain barrier at a slow rate, but it was not eliminated easily from the brain. The accumulation of aluminum touched the threshold concentration inducing multiple manifestations of clinical and pathophysiological toxicity to the brain. In order to prevent Al toxicity humans must prevent the metal accumulation by reduced use of Al, which is of crucial importance. Awareness of the effects of Al is the primary factor in preventing Al-induced toxicity.

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