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# CYTOGENETIC STUDIES ON THE EFFECTS OF ALUMINUM CHLORIDE AND THE PROTECTIVE ROLE OF VITAMIN C IN MICE

BY

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## ABSTRACT

Although AlCl<sub>3</sub> is widely used, research has attached various side effects to them. The aim of this study was to investigate the cytogenetic effects of AlCl<sub>3</sub> in mice and the protective role of vit. C against these effect. Fifty-six Swiss albino mice were exposed to AlCl<sub>3</sub> alone or in combination with vit. C at doses of 400 mg/kg b.wt. (1/10 LD<sub>50</sub>), 800 mg/kg b.wt. (1/5 LD<sub>50</sub>) for 24 and 48 hrs and 200 mg/kg b.wt. (1/20 LD<sub>50</sub>) for 3 months (chronic treatment), vit. C was used with the different doses of AlCl<sub>3</sub> at a dose of 10 mg/day. Bone marrow samples at different times (24, 48 hrs and three months respectively) were obtained. The results showed that AlCl<sub>3</sub> increase the number of structural and numerical chromosomal aberrations. AlCl<sub>3</sub> also decrease the rate of cell division (mitotic index) at (24, 48 hrs and three months respectively). Moreover, the use of vit. C gave promising results against AlCl<sub>3</sub> toxicity as it significantly decreased the frequency of chromosomal aberrations.

# **INTRODUCTION**

Aluminum (Al) was considered as a non toxic element until the 1970s when evidence came up indicating that aluminum induced morphological changes in the cells of the nervous system resembling those occurring in Alzheimer's disease (Lechmann, 1992). The average human Al intake through food and beverages has been reported to be in the range of 2.5–13 mg/day. However, it varies with food composition, country/place of residence, age and sex (WHO/IPCS, 1997). Al metal has numerous applications including the manufacture of

kitchen utensils, food and drink packaging, baking powder, antiacids and as an anticoagulant of organic matter in water purification (Atli et al., 2006). The genotoxicity of AlCl<sub>3</sub> has been described by several studies showing that AlCl<sub>3</sub> has genotoxic effects including chromosomal aberration and sister chromatid exchanges (Hasan et al., 2011 and Sandrine et al., 2013). AlCl<sub>3</sub> has been demonstrated to decrease the number of cells that undergo mitosis (Xiu-Lan et al., 1994). Genotoxic activity of AlCl<sub>3</sub> may be due to induction of oxidiezed DNA bases that may be converted into DNA breaks (Rao et al., 1993). Recent attention has focused on a number of water soluable vitamins such as vit. C. This vitamin is one of major dietary antioxidant in the body (Byers and Guerrero, 1995). It has been shown to prevent lipid peroxidation, reduced accumulation of free radicals and their hazardous action (Yosef, 2004).

The present study was therefore carried out to investigate the cytotoxic effects of exposure to AlCl<sub>3</sub> in mice and the possible protective effects of vit. C against these effects.

# **MATERIALS AND METHODS**

#### **Tested compounds:**

AlCl<sub>3</sub> was obtained from (LOBA Chemie Co, Maharashtra, India) and vit. C was obtained from (Al-Alamia Chemicals Co, Alexandria, Egypt).

# **Experimental animals and design:**

Fifty-six Swiss albino mice *(Mus musculus)* were obtained from experimental animal farm in Helwan city and were used in this study. They were 8-10 weaks old and weighted 20-25 g at the beginning of the experiment. Pelleted ration and water were offered ad-libitum. Thirty-six mice were used in acute treatment and were divided into six experimental groups each of six animals (Table 1). Doses of treatment were calculated according to **(Chinoy and Bhattacharya, 1997 and Anirudha et al., 1998).** AlCl<sub>3</sub> was injected intraperitoneally, while vit. C was given in drinking water one week before the injection of AlCl<sub>3</sub>. Twenty mice were used in chronic treatment and were divided into four groups each of five animals. In chronic treatment AlCl<sub>3</sub> and vit. C were given orally in diet for three months (Table 2).

Group	Treatment	Dose	No. of animals
1	Control	-	6
2	Vit C	10 mg/day	6
3	AlCl <sub>3</sub>	1/10 LD <sub>50</sub> (400 mg/kg b.wt.)	6
4	AlCl <sub>3</sub> and vit C	$1/10 \ LD_{50}$ (400 mg/kg b.wt.) and $10 \ mg/day$	6
5	AlCl <sub>3</sub>	1/5 LD <sub>50</sub> (800 mg/kg b.wt.)	6
6	AlCl <sub>3</sub> and vit C	1/5 LD <sub>50</sub> (800 mg/kg b.wt.) and 10 mg/day	6

Table (1). Experimental design of acute study (24 and 48 hrs) to AlCl<sub>3</sub>:

Table (2). Experimental design of chronic study (3 months) to AlCl<sub>3</sub>:

Group	Treatment	Dose	No of animals
1	Control	-	5
2	Vit C	10 mg/day	5
3	AlCl <sub>3</sub>	1/20 LD <sub>50</sub> (200 mg/kg b.wt.)	5
4	AlCl <sub>3</sub> and vit C	1/20 LD <sub>50</sub> (200 mg/kg b.wt.) and 10 mg vit C /day	5

# Sample collection and preparation:

At the end of the experimental period all animals were injected intaperitoneally with 4 mg/kg b.wt. of aquoeus solution of colchicine two hours before the time of the sacrifice. Bone marrow was preparated for the analysis of chromosomal aberrations in metaphase cells according to the techniques of **Ford and Hamerton**, (1956). Fifty metaphase cells per animal were analyzed in order to determine the frequencies of chromosomal aberration. From each group 3000 cells were analyzed to calculate the mitotic indices according to the equation of (**Brusick**, 1980).

$$MI = \frac{No.of dividing cells}{Total No of cells} \times 100$$

The differences in chromosomal abnormalities between different treatments were statistically tested using one way analysis of variance (SPSS, 2004) and M-state software packages. The differences in mitotic indices between treatments were statistically tested using Chi-square for independence by means of 2X2 contingency table (SAS, 2002).

# RESULTS

#### I. Chromosomal aberrations:

#### I.1. Twenty-four hours (24 hrs) treatment

Means  $\pm$  SE of total aberrant metaphase cells in control and treated groups were presented in (Table 3). The results showed that there was a significant difference between the control group and group given vit. C only (17.98 $\pm$ 1.5 and 15.33 $\pm$ 1.2). There was also a significant difference between the treated and the control groups. On the other hand, there was a non significant difference between the group treated with 1/10 LD<sub>50</sub> of AlCl<sub>3</sub> + vit. C and 1/5 LD<sub>50</sub> of AlCl<sub>3</sub> + vit. C (29.88 $\pm$ 0.88 and 31.00 $\pm$ 1.2) while there was a significant difference between the group treated with 1/10 LD<sub>50</sub> of AlCl<sub>3</sub> and 1/10 LD<sub>50</sub> of AlCl<sub>3</sub> + vit. C (34.67 $\pm$ 0.88 and 29.88 $\pm$ 0.88). Moreover, there was a significant difference between the group treated with 1/5 LD<sub>50</sub> of AlCl<sub>3</sub> and 1/5 LD<sub>50</sub> of AlCl<sub>3</sub> + vit. C (35.00  $\pm$  1.45 and 31.33  $\pm$  0.88).

111.5.				
Group	No. of animals/group	No. of examined cells/animal	Aberrant cells (means ±SE) in 24 hrs	Aberrant cells (means ±SE) in 48 hrs
Control	3	50	17.98±1.5 <sup>c</sup>	17.33±0.88 <sup>d</sup>
Vit. C	3	50	15.33±1.2 <sup>d</sup>	16.56±0.57 <sup>d</sup>
AlCl <sub>3</sub> 1/10 LD <sub>50</sub>	3	50	34.67±0.88 <sup>a</sup>	33.94±0.57 <sup>b</sup>
AlCl <sub>3</sub> 1/10 LD <sub>50</sub> + vit. C	3	50	29.88±0.88 <sup>b</sup>	31.00±0.33°
AlCl <sub>3</sub> 1/5 LD <sub>50</sub>	3	50	35.33±1.00 <sup>a</sup>	36.33±0.58 <sup>a</sup>
AlCl <sub>3</sub> 1/5 LD <sub>50</sub> + vit. C	3	50	31.00±1.2 <sup>b</sup>	32.03±0.88 <sup>b</sup>

**Table (3).** Means of aberrant cells in animals received AlCl<sub>3</sub> and/or vit. C for 24 hrs and 48 hrs:

Means having different letters in each period are significantly different at the level of P < 0.05.

#### I.2. Fourty-eight hours (48 hrs) treatment:

Means  $\pm$  SE of total aberrant cells of control and treated groups for 48 hrs are presented in (Table 3). The result showed that there was a significant difference between the control group and group given vit. C only at one side and the treated groups at the other side. However, no significant difference was observed between the two control groups. There was also no significant difference between groups treated with 1/10 LD<sub>50</sub> and 1/5 LD<sub>50</sub> of AlCl<sub>3</sub> + vit. C (33.94  $\pm$  0.57 and 32.03  $\pm$  0.88). There were however, a significant difference between the groups treated with 1/10 LD<sub>50</sub> of AlCl<sub>3</sub> + vit. C (33.94 $\pm$ 0.57 and 32.03  $\pm$  0.88). There were however, a significant difference between the groups treated with 1/10 LD<sub>50</sub> and 1/10 LD<sub>50</sub> of AlCl<sub>3</sub> + vit. C (33.94 $\pm$ 0.57 and 31.00 $\pm$ 0.33), and between groups treated with 1/5 LD<sub>50</sub> and 1/5 LD<sub>50</sub> of AlCl<sub>3</sub> + vit. C (36.33 $\pm$ 0.58 and 32.03 $\pm$ 0.88). The 1/5 LD<sub>50</sub> of AlCl<sub>3</sub> showed the highest mean for aberrant cells (36.33 $\pm$ 0.58).

#### I.3. Chronic (3 months) treatment:

Means  $\pm$  SE of total aberrant metaphase of control and treated groups were presented in (Table 4). These results showed that there were no significant difference in chromosomal aberrations between control group and group given vit. C only (15.33 $\pm$ 0.23 and 16.46 $\pm$ 1.74). On the other hand, there were a significant difference between the control groups and AlCl<sub>3</sub> treated groups. There were also a significant difference in aberrant cells between the AlCl<sub>3</sub> treated group and group treated with AlCl<sub>3</sub> + vit. C (36.67 $\pm$ 0.88 and 29.00 $\pm$ 0.33).

The different types of chromosomal aberrations showed in acute and chronic treatment were presented in figures (2-9).

Table (4). Means of aberrant cells in animals received AlCl<sub>3</sub> and/or vit. C for three months:

Group	No.of animals/group	No.of examined cells/animal	Aberrant cells (means± SE)	
Control	5	50	15.33±0.23°	
Vit. C	5	50	16.46±1.74 <sup>c</sup>	
AICl <sub>3</sub> 1/20 LD <sub>50</sub>	5	50	36.67±0.88 <sup>a</sup>	
AlCl <sub>3</sub> 1/20 LD <sub>50</sub> + vit. C	5	50	29.00±0.33 <sup>b</sup>	

Means having different letters in each period are significantly different at the level of P < 0.05.



Fig (1): Normal metaphases chromosomes of mice bone marrow cells.

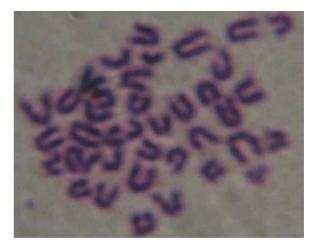


Fig (2): Metaphase chromosomes of mice bone marrow cells after aluminum chloride 1/10 LD<sub>50</sub> treatment showing (a, b): Chromatid deletion and (c, d): Chromatid gap.

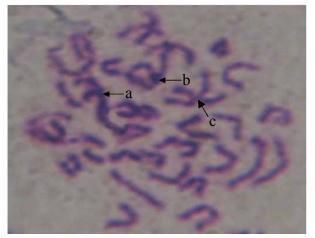


Fig (3): Metaphase chromosomes of mice bone marrow cells after aluminum chloride 1/10 LD<sub>50</sub> treatment showing (a, b): Stickness and (c): Centric fusion translocation.



Fig (4): Metaphase chromosomes of mice bone marrow cells after aluminum chloride 1/10 LD<sub>50</sub> + vit. C treatment showing centromeric

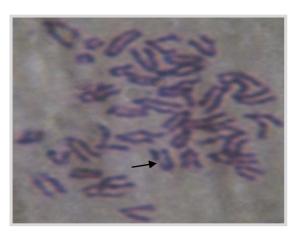


Fig (5): Metaphase chromosomes of mice bone marrow cells after aluminum chloride  $1/10 \text{ LD}_{50}$  + vit. C treatment showing chromatid break.

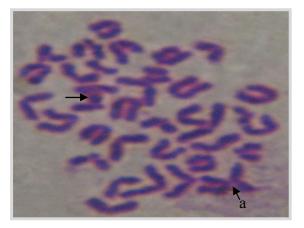


Fig (6): Metaphase chromosomes of mice bone marrow cells after aluminum chloride  $1/10 \text{ LD}_{50}$  + vit. C treatment showing (a) chromosome fragment and (b) centric fusion translocation.



Fig (7): Metaphase chromosomes of mice bone marrow cells after aluminum chloride 1/5 LD<sub>50</sub> treatment showing ring chromosome.

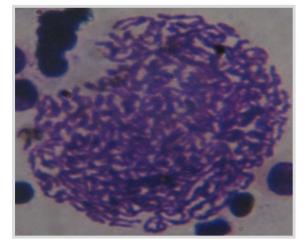


Fig (8): Metaphase chromosomes of mice bone marrow cells after aluminum chloride 1/5 LD<sub>50</sub> treatment showing polyploidy.

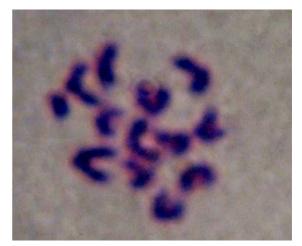


Fig (9): Metaphase chromosomes of mice bone marrow cells after aluminum chloride  $1/5 \text{ LD}_{50}$  + vit. C treatment showing hypoploidy.

# II. Mitotic index:

#### **II.1.Twenty-four hours (24 hrs) treatment:**

Chi square analysis showed that there was a significant difference among the control and treated groups at 24, 48 hrs and three months of treatment (Tables 6, 8 and 10).

Group	Total No. of examined cells	No. of divided cells	No. of non divided cells	M.I
Control	3000	144	2856	4.80
Vit. C	3000	132	2868	4.40
Aluminum chloride 1/10 LD <sub>50</sub>	3000	78	2922	2.60
Aluminum chloride 1/10 LD <sub>50</sub> + vitamin C	3000	92	2908	3.06
Aluminum chloride 1/5 LD <sub>50</sub>	3000	61	2939	2.03
Aluminum chloride 1/5 LD <sub>50</sub> + vitamin C	3000	84	2916	2.80

Table (5). Mitotic indices in animals received aluminum chloride and /or vit. C for 24 hrs.

**Table (6).** Chi square values of mitotic indices in animals received AlCl3 and /or vit. C for24 hrs:

Group	Chi square value						
	Control	Vit. C	1/10 LD <sub>50</sub> of AlCl <sub>3</sub>	1/10 LD <sub>50</sub> of AlCl <sub>3</sub> + vit. C	1/5 LD <sub>50</sub> of AlCl <sub>3</sub>	1/5 LD <sub>50</sub> of AlCl <sub>3</sub> + vit. C	
Control	-	-	-	-	-	-	
Vit. C	0.45	-	-	-	-	-	
AICl <sub>3</sub> 1/10 LD <sub>50</sub>	19.76**	13.86**	-	-	-	-	
AlCl <sub>3</sub> 1/10 LD <sub>50</sub> + vit. C	11.47**	7.05**	1.023	-	-	-	
AICl <sub>3</sub> 1/5 LD <sub>50</sub>	33.96**	26.23**	1.88	6.03*			
AlCl <sub>3</sub> 1/5 LD <sub>50</sub> + vit. C	15.87**	10.60**	0.15	0.28	3.42		

\* Chi square values are significantly different at the level P< 0.05.

\*\*Chi square values are highly significant different at the level P<0.01

# .2. Fourty-eight hours (48 hrs) treatment:

Group	Total No. of examined cells	No. of divided cells	No. of non divided cells	M.I
Control	3000	124	2876	4.13
Vit. C	3000	141	2859	4.70
Aluminum chloride 1/10 LD <sub>50</sub>	3000	65	2935	2.16
Aluminum chloride 1/10 LD <sub>50</sub> + vitamin C	3000	90	2910	3.00
Aluminum chloride 1/5 LD <sub>50</sub>	3000	60	2940	2.00
Aluminum chloride 1/5 LD <sub>50</sub> + vitamin C	3000	81	2919	2.70

 Table (7). Mitotic indices in animals received aluminum chloride and /or vit. C for 48 hrs.

 Table (8). Chi square values of mitotic indices in animals received AlCl3 and /or vit. C for 48 hrs:

	Chi square value							
Group	Control	Vit. C	1/10 LD <sub>50</sub> of AlCl <sub>3</sub>	1/10 LD <sub>50</sub> of AlCl <sub>3</sub> + Vit. C	1/5 LD <sub>50</sub> of AlCl <sub>3</sub>	1/5 LD <sub>50</sub> of AlCl <sub>3</sub> + vit. C		
Control	-	-	-	-	-	-		
Vit. C	1.01	-	-	-	-	-		
1/10 LD <sub>50</sub> of AlCl <sub>3</sub>	18.37**	28.27**	-	-	-	-		
1/10 LD <sub>50</sub> of AlCl <sub>3</sub> + vit. C	5.27**	11.25**	3.81	-	-	-		
1/5 LD <sub>50</sub> of AlCl <sub>3</sub>	22.25**	32.94**	0.13	5.75*		-		
1/5 LD <sub>50</sub> of AlCl <sub>3</sub> + vit. C	8.90**	16.28**	1.57	0.38	2.90	-		

\* Chi square values are significantly different at the level P < 0.05.

\*\* Chi square values are highly significant different at the level P<0.01.

## **II.3.** Chronic (3 months) treatment:

Table (	9). Mitotic	indices	n animals	received	aluminum	chloride	and /or	vit.	C for	three
	months	5.								

Group	Total No. of examined cells	No. of divided cells	No. of non divided cells	M.I
Control	3000	147	2853	4.90
Vitamin C	3000	153	2847	5.1
Aluminum chloride 1/20 LD <sub>50</sub>	3000	77	2923	2.56
Aluminum chloride 1/20 LD <sub>50</sub> + vitamin C	3000	111	2889	3.71

Table (10). Chi square values of mitotic indices in animals received AlCl<sub>3</sub>

and /or vit	C for three	months:
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	Chi square value					
Group	Control	Vit. C	1/20 LD <sub>50</sub> of AlCl <sub>3</sub>	1/20 LD <sub>50</sub> of AlCl <sub>3</sub> + vit. C		
Control	-	-	-	-		
Vit. C	0.08	-	-	-		
1/20 LD <sub>50</sub> of AlCl <sub>3</sub>	22.07**	25.43**	-	-		
1/20 LD <sub>50</sub> of AlCl <sub>3</sub> + vit. C	4.96*	6.66**	5.97*	-		

\* Chi square values are significantly different at the level P< 0.05.

\*\* Chi square values are highly significant different at the level P<0.01.

# DISCUSSION

The results of exposure to AlCl<sub>3</sub> indicated that treatment with AlCl<sub>3</sub> for 24, 48 hrs and three months caused a significant increase in the occurrence of chromosomal aberrations. **Rao** et al., (1993) found that Al caused genetic malfunction through irreversibe unwinding of DNA and accumulation of cells in S-phase. These findings agree with those of Yumei et al., (1988) on human lymphocytes. Similar results were obtained by Moreno et al., (1997). The

present findings are also in agreement with those reported by Yang Yong et al., (2005) who found that adding aluminum chloride to drinking water for 100 days caused significant damage to DNA. The results of Anna et al., (2006) showed that AlCl<sub>3</sub> induced significant increase in the level of DNA damage in blood lymphocytes are also in accordance with obtained results. The results are also in accordance with the findings of Zeinab, (2007) in rat bone marrow cells treated with aluminum hydroxide for 30 days, and that of Di Virgilio et al., (2010) in Chinese hamster ovary cells (CHO-K11ine) treated with aluminum hydroxide for 24 hrs. And, Hasan et al., (2011) in rats treated with AlCl<sub>3</sub> for 4 consecutive days. The results of this work are also in agreement with those of Sandra et al., (2013) in human blood lymphocyte received aluminum phosphide at 72 hrs. On contrary, these results disagree with those obtained by Trippi et al., (2001) who reported that Al was not observed to increase the micronucleus frequency in brain cells of Parkinso'n diseased patient.

The obtained results showed that vit. C has a protective effects, decreasing the frequency of chromosomal aberrations produced by AlCl<sub>3</sub>. These results are in accordance with those of **Prasad et al.**, (2010) in mice bone marrow injected with cyclophosphamide, those of **Amal and Fawzy**, (2012) in rats treated with cadmium for 90 days and those of **Das et al.**, (2013) when vit. C was used prior to metronidazole treatment.

From the obtained results it could be stated that AlCl<sub>3</sub> decreased mitotic index after 24, 48 hrs and 3 months. These results agree with those of **Xiu-Lan et al.**, (1994) in human blood cultures treated with AlCl<sub>3</sub>. Also **Dong and Wusheng**, (2001) in root tip cells of Zea mays L treated with AlCl<sub>3</sub> at different concentrations (101, 102, 103, 104, 105 M).

On contrary, these results disagree with the results of **Balasubramanyam et al., (2009)** in Wistar rats treated with aluminum oxide nanomaterials for 18 and 24 hrs and did not cause any significant reduction in mitotic index.

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# الملخص العربى دراسات وراثية خلوية لتأثير كلوريدالألومنيوم و كذلك الأثر الوقائي لفيتامين ج في الفئران

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بالرغم من أن كلوريد الألومنيوم تستخدم الأن علي نطاق واسع إلا أن الأبحاث الحديثة أكدت أن لهذه الأملاح آثار جانبية عديدة. ولهذا أجريت هذه الدراسة لتوضيح التأثير الغلوى السام لكلوريد الألومنيوم علي الفئران. وكذلك لتوضيح مدي قدرة فيتامين ج علي حماية الخلية من التأثير السام لكلوريد الألومنيوم. وعليه تم تصميم هذه التجربة من ٥٦ فأر تجارب تعرضوا لكلوريد الألومنيوم بمفرده أو مع فيتامين ج عند جرعات ٤٠٠ مج/ كجم وزن حي (١٠٠ من الجرعة المميتة للنصف) و ٢٠٠ مج محموزن حي (٥/١ من الجرعة الميتة للنصف) لمدة ٢٤ و٤٨ ساعة و د٢٠ مج/ كجم وزن حي (١٠٠ من الجرعة المعتة للنصف) لمدة ثلاثة أشهر. فيتامين ج استخدم مع الجرعات المختلفة من كلوريد وزن حي (١٠٠ من الجرعة المميتة للنصف) لمدة ثلاثة أشهر. فيتامين ج استخدم مع الجرعات المختلفة من كلوريد الألومنيوم بجرعة ١٠ مج/اليـوم. وقد أوضحت النتائج أن كلوريد الألومنيوم له قدرة علي زيادة التشوهات الكروموسومية العددية والتركيبية. أوضحت النتائج أن كلوريد الألومنيوم له قدرة علي زيادة التشوهات الكروموسومية العددية والتركيبية. أوضحت النتائج أيضا أن كلوريد الألومنيوم له قدرة علي زيادة التشوهات المروموسومية العددية والتركيبية. أوضحت النتائج أيضا أن كلوريد الألومنيوم له تأثيرضار علي معدل الإنقسام المروموسومية العددية والتركيبية. أوضحت النتائج أيضا أن كلوريد الألومنيوم له تأثيرضار علي معدل الإنقسام الميتوزي لخلايا نخاع عظام الفئران عند ٢٤ اله الماء وثلاثة أشهر. وأن إستخدام فيتامين ج أدي إلي نتائج جيدة ضد التأثير الضاراركلوريد الألومنيوم حيث أنه أدي إلي تقليل معدلات التغيرات الكروموسومية في الفئران