Teratogenic Nephrotoxicity induced by Aluminium

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The intensified growth of the modern industry has been accompanied by an increased utilization of metals in the processing of manufactured goods, foods and drugs. The mobilization of many trace elements has resulted in a growing concern about the effects of these substances on various biological processes especially about their possible effects on early mammalian development Hardness of drinking water has positively been correlated to lethal congenital malformations. Chemical agents and pharmaceutical drugs play a very important role in the teratogenesis. Amongst other trace elements or environmental chemicals, aluminium has been reported to have teratogenic properties i n c hick a nd r ats. S o t he p resent s tudy w as c arried o ut t o e stablish t he r ole o f aluminium containing compounds in producing intra-uterine growth retardation and defected renal development, when the pregnant mothers use these compounds for various periods during pregnancy.
Key Word: Aluminium, Nephrotoxicity, teratogenicity.

Humans are continuously exposed to aluminium as this element is widely distributed in nature. Its daily intake varies from person to person and country to country because it not only depends upon personal liking or disliking but also upon geochemistry of that particular area. 6mg per day is considered as an average daily intake of aluminium in normal routine diet[1]. Out of this only few micrograms per day is absorbed because of gastrointestiral barrier. However absorption barrier can be overcome when large loads are given orally in the form of antacids[2] or parenteraly[3]. Under these circumstances large quantities of aluminium are retained in body[4]

Aluminum is a metal of increasing clinical importance because of its biological actions and its toxicity which develops on its accumulation in the tissue of the patients on total parenteral administration[5] in infants and children with immature or impaired renal functions who has been on treatment with oral aluminium-containing phosphate binding agents[6]

Even normal infants taking aluminium-containing antacids show increased tissue loads[7]. Ittel et.al[8] (1991) have experimentally proved the enhancement of toxicity of aluminium containing antacids in critically ill patients with or without renal impairment. Aluminium is present in large quantities in infant formulae[9] . In experimental animals following aluminium loading, it accumulates not only in bone and brain tissue but also in liver, kidney and muscle tissues including the heart[10]

Aluminium has a number of biological effects. It promotes the reaction between Cytochrome C and succinic dehydrogenase and is a nessary co-factor for the activation of guanine nuecleotide-building regulation protein by flouride, for the stimulation of adenylate cycase activity[11] It has an inhibitory effect on bone-phosphatases, hexokinases[12, 13] and enhances the activity of cholinestrases[12]. Aluminium has also been shown to displace magnesium from ATP[13], the resulting stablization of ATP Prevents phosphate transfer by Na+-K+-ATPase

[12]. It also binds calmodulin[14] and inhibits ferroxidase (ceruloplasmin) activity[15, 16].

Because of increasing use of aluminium pans and other cooking utensils in Pakistan and frequent use of antacids during pregnancy, it is more likely that pregnant mothers ingest more aluminium than normal daily dietary intake. This overload may lead to impaired renal development in the growing tissues.

The present study was carried out to establish the teratogenicity of aluminum compounds and to provide useful information and guideline for correct use of aluminum containing compounds during different trimesters of pregnancy.

Materials and methods

72 female and 36 male albino mice were used for the present study. Animals were kept (in the animal house of Postgraduate Medical Institute, Lahore) i n s eparate c ages and f ed w ith c ommercially p repared c hick-feed No.3 and water ad libitium. Care was taken regarding maintenance of optimum light and temperature in the animal room.

Mating was allowed in dark. Presence of vaginal plug was considered as a sign of conception and the day was taken as day 1 of pregnancy. The salt of aluminium used for the present study was $Al_2(SO_4).16H_2O$. 0.7mg/100gm body weight was the daily intraperitoneal dose used in the experiment. Average weight of animals was 50gm.

Experimental design

Pregnant female mice were divided at random into 6 control and 6 experimental groups. Control group animals were labeled A, B, C, D, E and F and given daily intraperitoneal injections of distilled water for various periods (Table 1). The animals of experimental group were also d ivided i nto subgroups A1, B1, C1, D1, E1 and F1, each comprising 6 pregnant animals. Each mouse was given daily intraperitoneal injection o f 0 .7-mg/100 g rams B.W. of Aluminum sulphate for periods given in Table.1. All animals were sacrificed on day 20 of gestation.

Table 1: Experimental Design

Control Group	Dose	Period	Experimental Group	Dose	Period
A	0.25ml of dist water	1-6	A₁	0.25ml of $Al_2(SO_4)_3$ solution	1-6
B	-do-	7-12	B₁	-do-	7-12
C	-do-	13-18	C₁	-do-	13-18
D	-do-	1-12	D₁	-do-	1-12
E	-do-	7-18	E₁	-do-	7-18
F	-do-	1-18	F₁	-do-	1-18

Days of gestation.

Recovery, fixation and preservation of embryos

On day 20 of pregnancy the animals were sacrificed. The embryos along with uteri were then fixed in buffered formalin. Forty-eight hours after fixation, kidneys of each embryo from each group were then processed as per routine. The sections were stained with Harris's Haemotoxyline and Eosin stain and studied under light microscope. Selected sections were then photographed.

Results

Embryos recovered from control groups showed typical histological structure of the kidney. The parenchyma was divided into cortex and medulla. The renal corpuscles were numerous and completely formed in the region of cortex. The lining epithelium of Bowman's capsule was flat. The nucleus was rounded and placed in the center. The urinary space was 0.1020-0.1025 mm in width. The proximal and distal convoluted tubules were lined by continuous epithelium varying from columnar to cuboidal in nature. The lumen of both the tubules was narrow. All the renal vessels were well formed.

The renal capsule was thin and easily tear able in almost all the treated groups except group A1. Renal parenchyma was clearly divided into cortex and medulla in groups A1, B1, C1, and D1. In groups E1 and F1 there was no clear-cut demarcation in cortex and medulla.

Discussion

The embryos recovered from the mothers who received dose for longer period showed some pathological changes in their kidneys. The changes were almost same in all the groups. They varied only in their extent. The pathological changes observed were

1. Hemorrhages and congestion of renal architecture more marked in the vicinity of glomeruli. (Fig-1)
2. Tubular degeneration and cyst like dilatation of renal tubules. (Fig-1 & 2)

The demarcation of renal parenchyma in cortex and medulla was quite prominent in all the groups except group E1 and F1. The urinary corpuscles were well formed with normal urinary spaces in-group A1. The width of the urinary space was increased in groups B1, C1, D1 & E1. In-group F1, no well-formed glomerulus was found, the cells were present only in clusters without any well-defined urinary space.(Fig-3)

The renal cortex showed overall congestion and hemorrhages in groups B1 C1 D1 E1 & F1. These hemorrhages were more marked in periglomerular region. No such change was observed in-group A1. The lining epithelium was simple squamous in all the treated groups. Congestion was more marked in cortical as compared to medullary region. The proximal and distal tubules showed vacuolar degeneration of varying intensity in all the treated groups, except A1. Groups B1 & C1 showed vacuoles in cells of proximal and distal tubules but the basement membrane remained intact. In groupD1, the vacuolar degeneration was present along with broken basement membrane at various places. In-group E1, the renal tubular architecture was missing at quite some places. In-group F1, there was complete loss of renal architecture. The cells were irregularly arranged in the form of a reticulum, both in cortex as well as in medulla. The intensity of all these changes was directly proportional to duration of exposure.
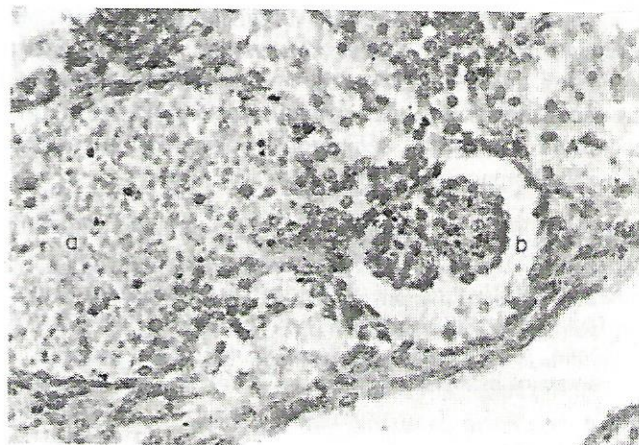

Fig. 1. histological section of kidney of embryo of C1. a) Periglomerular hemorrhage b) Increased width of urinary space.
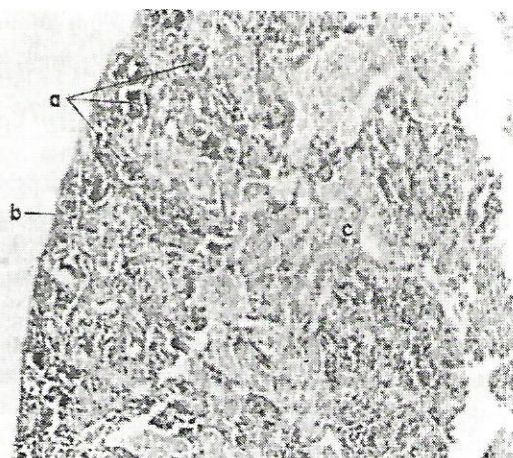

Fig-2 A histological section of kidney of embryo of E1. a) Poorly formed glomeruli b) Broken renal capsule c) Tubular degeneration.
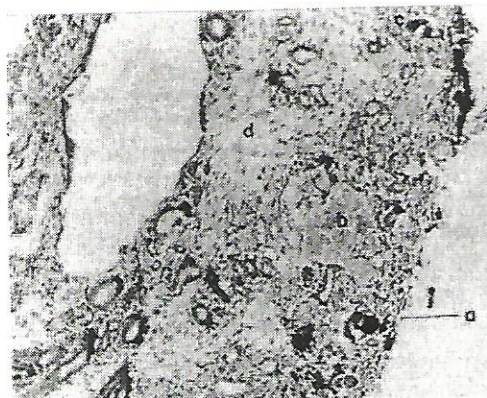
Fig.3 A histological section of kidney of embryo of F1. a) Deficient renal capsule b) Hemorrhagic spot c) Poorly formed glomeruli d) Area of complete tubular degeneration.

Conclusion

The conclusion drawn from the present study is that the aluminum containing compounds are very hazardous to mammalian embryos specially when these are used during organogenic period. The use of these compounds therefore be carried out very carefully. Pregnant population and growing children in particular should be protected. Moreover guidelines for the manufacturers can be formulated, keeping these results in view to save our future generations from the deleterious effects of aluminum containing compounds.

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