Original Article

Study the Increase of Brain Toxicity in Newborn Rats and Related to Exposure of Their Mothers to Uranyl Acetate

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Abstract

Background: Malformations of fetuses and congenital anomalies were observed in infants' brains with deformities. The current study aimed to investigate the effects of uranyl acetate on the chemical and oxidative status in mothers and its effects in many areas of the rat's newborn brain. **Materials and Methods:** Twenty-four adult female rats were treated with a single oral dose of 75 mg/kg uranyl acetate dihydrate (UAD) two weeks before mating and throughout the pregnancy and lactation period. The chemical and oxidative status of mothers was measured. Newborns were sacrificed at the 3rd and 5th weeks of age, and the brain was collected. **Results:** In mothers, there was a significant increase in chloride levels in the UAD-treated group compared to the control group, with no significant differences in Na^+ levels. Malondialdehyde (MDA) levels were significantly increased, and glutathione (GSH) levels were significantly decreased in the treated group. Histopathological changes in 3-week-old newborns included blood vessel congestion and astrocyte hypertrophy. In 5-week-old newborns, brain sections showed vacuolation in neuron cells, nuclear shrinkage, and oedema. **Conclusion:** Uranyl acetate affects sodium and chloride levels and induces oxidative stress, causing histological defects in the brains of newborn rats.

Keywords: Brain toxicity, glutathione, malondialdehyde, rat, uranyl acetate

Introduction

Toxic mechanisms of the action potential of uranyl acetate dihydrate (UAD) included genotoxicity and mutagenicity, inhibition or changes in the synthesis of protein or steroid, messed up in division of the cell, enzyme systems inhibition or disturbance, also normal reproduction behavioural patterns disruption(1). Uranyle acetate is a uranium salt commonly used in electron microscopy and some laboratory procedure; uranium moves across the blood–brain barrier(2). Implanted UAD pellets for rats, lead to the UAD distributed heterogeneously, also reached the central nervous system (CNS)(3).

The result of each mechanism perhaps causes cell death raised or decreased; contact of cell-to-cell to deranged; biosynthesis reduced; pattern of morphogenetic formation increased; also tissue structure disruption which may be result pathogenesis abnormality in the foetus(4). One of many studies in Iraq which recorded persons contaminated by UAD were 54.5% in Abu-Graib and Al-Taji, also recorded raised level percentage who deal directly derivates of uranium(5). Among live births defects types of CNS were common mostly to birth defects. About 4.6, 4.35 and 8.4/1000 live births have rate 55% in Al-Anbar, Basrah and Diwaniyah, respectively, for the period 1999–2000; also, for each 1000 live births nearly 4.48 in Erbil(6,7). Newly, the same per cent of defects in neural tube from Iraq, Duhok and Baghdad were reported at 4.7 and 5.95/1000 live births(8,9).

Plasma UAD in animals was substantial fraction which associated with low-molecular-weight fraction ultra-filterable, also weakly associated of the remainder with other plasma proteins and transferrin. Mostly, 0.7% of UAD were leaving, the red blood cells were attached to plasma(10).

Uranium appears rapidly in the circulatory system after ingestion which is primarily associated with the red cells(11).

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Limited study of implanted with UAD pellets in rats, which was appear that UAD crosses through the placental barrier and enters the tissue of foetus(12). Most studies on uranium-induced toxicity of development experimentally used many types of mammal species(13).

Promoted oxidative stress in cerebral tissues was shown due to accumulated of UAD in the hippocampus, cortex and cerebellum, which the level of thiobarbituric acid reactive substances was correlated positively with the content of UAD, instead of that in cerebellum the levels of glutathione (GSH) also oxidised glutathione were negatively and positively, respectively, correlated with concentrations of UAD. The concentration of U in the hippocampus was correlated positively with catalase as well as superoxide dismutase activities(14).

Studies on animals found that high doses of UAD can move across blood–brain barrier. In the implanted rats with UAD, found no evidence of neurotoxicity was appear(15).

Materials and Methods

Twenty-four albino rats (Dawley–Sprague), adult females, were used in this study with body weight average of 200–250 g and with old of 12–15 weeks. Baghdad University, the temperature was 25°C–28°C, fed normal rodent pellets ad Libitum with tap water and good ventilation.

The female was paired 2:1 male, the presence of sperm in the smear from the vagina indicated day 0 of gestation.

Stomach tube was used to administered adult females orally with UAD as a single dose by doses of 75 mg/kg(16) before collecting them with untreated males for 2 weeks, also during pregnancy as well as lactation period. At age 3rd and 5th weeks, newborn was taken from each group and animals were sacrificed and taken the brains directly.

Uranyl acetate preparation

Uranyl acetate powder (from Al-Nahrain University) dissolved in distilled water and administrated by 75 mg/kg/B wt(17).

Laboratory examination

After the animals (mothers) were ethically euthanised with chloroform at the end of the lactation period, blood was drawn from the heart and collected in a gill tube and the serum was separated and used as following:

1-serum levels of Na^+ and Cl

The technique of ion-selective electrode was used for serum samples to examine sodium level as well as chloride level, the Electrolyte Analyser of 9180 AVL(18).

2-determination of malondialdehyde and serum glutathione concentration

The serum malondialdehyde (MDA) concentration was examined due to Buege and Aust method.(19) The serum concentration of GSH was measured according to the Ellman method(20).

Study of histopathology

Brain specimens were fixed in formalin 10%, dihydrated in ethanol through ascending series, used Harris haematoxylin and eosin stain to stain with(21).

Statistical analysis

Analysis of statistical data was performed by basis analysis of variance using significant levels of ($P \leq 0.05$). Differences between groups were determined using the least significant differences as described by Buczyńska and Tarkowski(22).

Ethical Approval

Ethical approval for this study (P-G/ 1566) was provided by the Ethical committee of University of Baghdad/ College of Veterinary Medicine on 2 July 2024.

Results and Discussion

1-serum Na^+ level and Cl^- level

Results of Table 1 show that there appears to be a significant elevation in the uranyl acetate group in the level of Cl^- as compared to the group of control; also, there are no significant differences between the control and uranyl acetate group in sodium level.

2-oxidative status parameter

The oxidant–antioxidant induce is illustrated in Table 2. The results reveal that MDA levels were significantly increased ($P \leq 0.05$) in the uranyl group as compared to the control. Furthermore, the GSH level was significantly decreased in uranyl acetate groups compared with control group.

Most causes of defects of birth are still unclear, but recent research indicates that factors from the environment may be the reason for genetic mutations and interfere with genetic factors, potentially leading to birth defects(17).These defects mostly result from a combination of genetic and environmental

Table 1: Uranyl acetate effect on serum level of sodium and chloride

Parameters groups	Serum level parameters (mean±SE)	
	Sodium (meq/L)	Chloride (meq/L)
Control/D.W	135.50±0.97^a	79.79±1.07^b
Uranyl acetate	136.87±1.10^a	92.00±0.88^a

Different small letters are significantly different. Mean±SE. SE: Standard error, D.W: Distilled water

Table 2: Uranyl acetate on malondialdehyde and glutathione levels (oxidative status)

Parameters groups	Oxidative parameter (mean±SE)	
	MDA (µmol/L)	GSH (µmol)
Control/D.W	2.10±0.05^b	390.00±21.17^a
Uranyl acetate	6.55±0.38^a	205.00±6.79^b

Different small letters are significantly different. Mean±SE. SE: Standard error, D.W: Distilled water, MDA: Malondialdehyde, GSH: Glutathione

influences. The target organs are mainly kidneys to UAD toxicity(16), but it can also reach the brain(21).

Exchangers of anion may have low specificity anion and also can move a different anion number(23).

Demonstrated that Uranyl acetate exposure may change levels of antioxidants. MDA can produce from lipid peroxidation in cellular membranes, which process between free radicals and unsaturated fatty acids(24). Furthermore, it changes the activities of antioxidant enzyme and guides to raise of MDA as a mechanism of defence as a consequence of regular metabolic processes, a specific amount of reactive oxygen species (ROS) formed to maintain the balance is within generating and disposing of ROS this agreement with(25). The up-regulating defence of antioxidant response to elevate generation of ROS, in cellular metabolism detoxification for anti-oxidation the GSH have a crucial role in detoxification(26).The GSH decrease agrees with(26) which found that DU is an external source associated with different indicators of oxidative stress, such as increased ROS formation, lipid peroxidation and GSH depletion. Lipid peroxidation is indicated by elevated of MDA level.

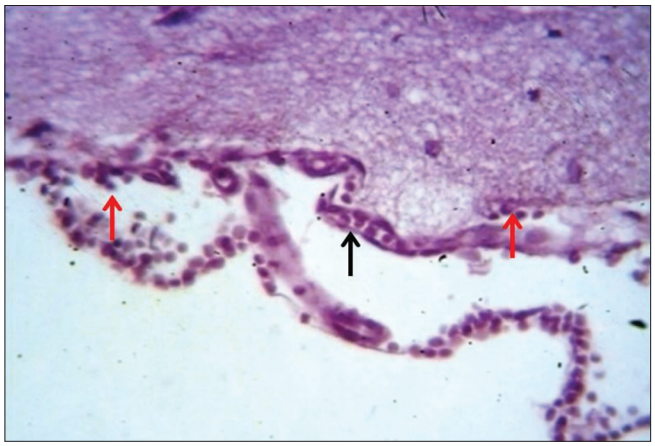

Figure 1: Brain section of newborn at 3rd week after administrated with 75 mg/kg appears meningitis characterized by thickening of pia matter with marked infiltration of mononuclear leukocytes (MNLs) and polymorphic nuclear leukocytes (red arrows) and vascular congestion (black arrow) (×400)

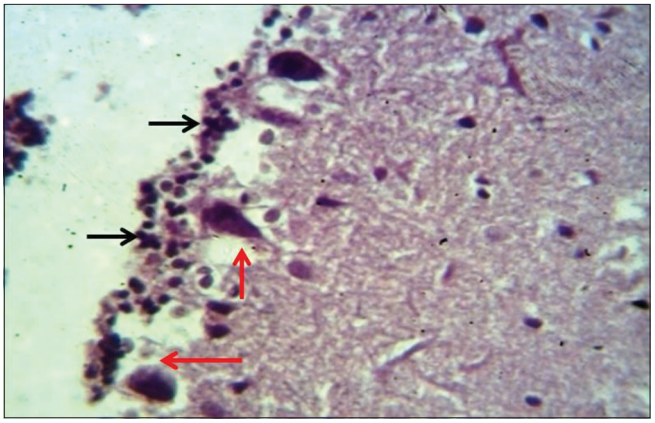

Figure 3: Brain section of newborn at 5th week after administrated with 75 mg/kg appears encephalitis characterized by moderate infiltration of mononuclear leukocytes (MNLs) (Black arrows), peri neurons edema (Red arrows) with marked nuclear pyknosis of neurons (×400)

Histopathological result

Changes of the brains of newborns histopathologically at 3rd week administrated by 75 mg/kg appear blood vessel congestion, brain parenchyma have astrocyte hypertrophy and hyperplasia, also aggregation of neutrophil in the lumen [Figures 1 and 2].

The brain section of 5th-week newborn administrated by 75 mg/kg appear to vaculation of neuron cells, nuclei shrinkage of it, also congestion blood vessel, neuron degeneration and oedema around the nerve cell, which is characterised by around of body cell in the parenchyma of the brain [Figures 3-5].

In the current study, the main exchanges in newborn brains at 3rd weeks, which were mother administrated by 75 mg/kg,

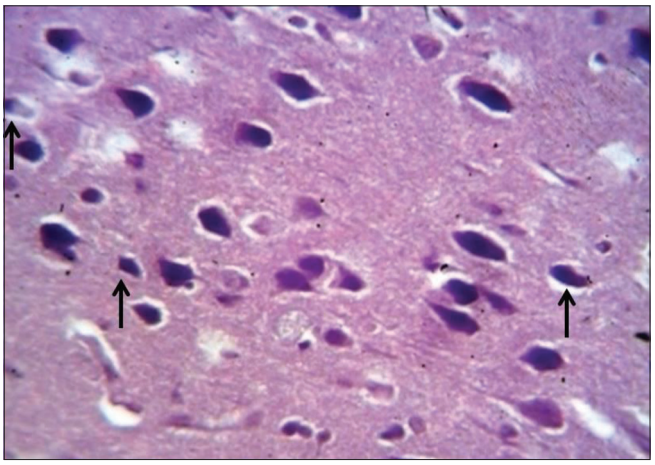

Figure 2: Brain section of newborn at 3rd week after administrated with 75 mg/kg appears marked nuclear pyknosis of pyramidal neurons and some glial cells (Arrows) (×400)

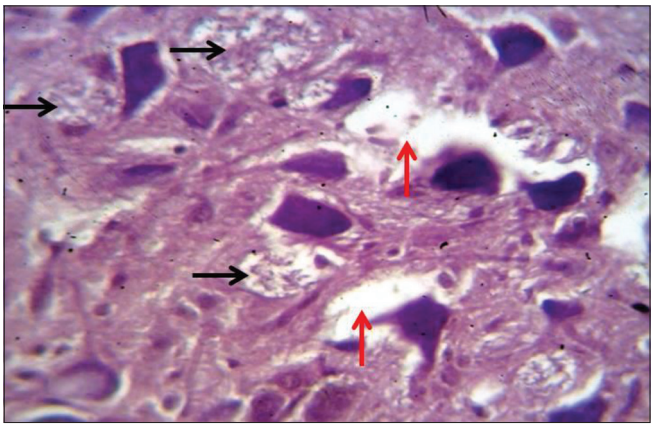

Figure 4: Brain section of newborn at 5th week after administrated with 75 mg/kg appears marked demyelination of axons, peri neurons edema (Red arrows) and nuclear pyknosis (Black arrows) of neurons (×400)

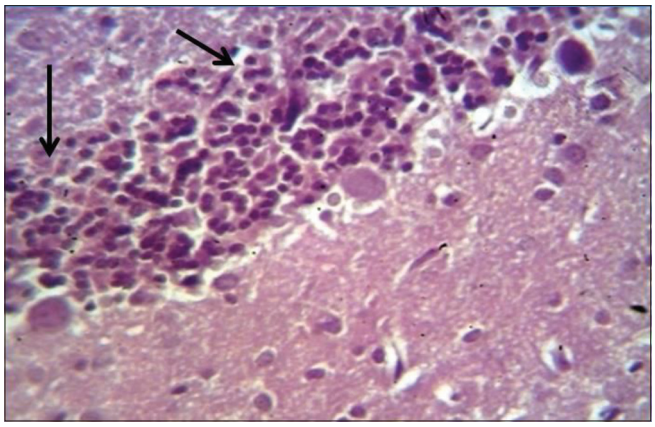

Figure 5: Brain section in newborn of 5th weeks after administrated of 75 mg per kg appear severe encephalitis characterized by severe infiltration of mononuclear leukocytes (mnls) (arrows) (x400)

were revealed Meningitis characterised by thickening of pia matter with marked infiltration of mononuclear leucocytes and polymorphic nuclear leucocytes and vascular congestion, nuclear pyknosis of pyramidal neurons and some glial cells. These findings indicate an inflammatory response within the meninges; furthermore, vascular congestion reflects inflammation-associated increased permeability, which can lead to complications like cerebral oedema, this agree with(27), also the pyknosis appeared that cell started in necrosis(28). According to Houpert *et al*.(24) how found uranium accumulated after UAD chronic ingestion, in hippocampus mainly.

The possibility raised with such data showing that the brain has some disturbances of neurology, although, until today, these changes (neurophysiological) had been in agreement with our explain. The UAD absorption depends on solubility in the GIT. In mice, uranium may cause bizarre inflammation in the renal, brain, pulmonary as well as other tissues and causes neurological effects(9), and this agrees with our result.

However, this study exhibits that the newborn brain at 5th week which their mother was administrated by 75 mg/kg Encephalitis characterised by moderate and severe infiltration of mononuclear leucocytes, peri neurons oedema with marked nuclear pyknosis of neurons, also marked demyelination of axons, this oedema increase intracranial pressure, pyknosis undergo necrosis of the cell and demyelination of axons decrease conductivity(27).

Conclusion

It could be concluded that uranyl acetate has a toxic effect on ions and oxidative stress status; also, it causes histological defects in the brain of newborns.

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Conflicts of interest

There are no conflicts of interest.

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