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Teratogenic effect of formaldehyde in rabbits

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Abstract

Thirty three pregnant rabbits were exposed to vapour of 10% formaldehyde (12 ppm) throughout the gestation period to know its effect on newborns. The results showed no abortion or foetal mortality but there were some anomalies (23.8%) among the newborns rabbits which includes: meromelia (6.8%), encephalocele (6.1%), Oligodactyly (4.1%), Umbilical hernia (3.4%) and Short tail (3.4%); besides that small for date and decrease in the body weight of the newborns were also noticed. These findings suggest that formaldehyde is a teratogenic agent.

Keyword: Formaldehyde, Teratogenicity, Rabbit.
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التأثير المسخي للفورملدهيد في الأرانب

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الخلاصة

عرض ثلاثة و ثلاثون من الارانب الحوامل الى (١٠%) من بخار الفورملدهيد (١٢ جزء من مليون) خلال طول مدة الحمل. النتائج أظهرت عدم وجود إجهاض أو نفوق للاجنة ولكن وجد بعض التشوهات الجنينية (٢٣,٨%) بين الولادات الحديثة والتي تمثلت بالاتي: صغر الاطراف (٦,٨%)؛ قيلة دماغية (٦,١%)؛ قلة عدد الاصابع (٤,١%)؛ فتق سري (٣,٤%) و ذيل قصير (٣,٤ %). بالاضافة الى ذلك لوحظ صغر حجم الوليد بالنسبة لفترة الحمل و نقصان الوزن. هذة النتائج توضح بأن الفورملدهيد مادة مسخية في الأرانب.

Introduction

Fomaldehyde is well known as a preservative, a sterilizer and embalming fluids; and approximately 2.1 million workers are exposed to formaldehyde (1,2). Domestic exposures occur mainly from consumer products that include textiles, insulation, paper, cosmetics and wood-products (3).

Formaldehyde exposure has toxic effects on respiratory system, gastrointestinal tract, heamopoitic tissue and nervous system (4-7). Reproductive and developmental effects are believed to be minimal (8-10).

Increased cryptochordism was investigated in pregnant rats following inhalational exposure to formaldehyde, while formaldehyde inhalation with bipyridyl administration showed cryptochordisim, syndactyly, adhesion of breastbone with tail, and phoecomelia (11). Congenital defects, included cryptochordism, delay in ossification of hyoid bone, delay in eruption of upper and lower incisors, as well as decrease in body weight were noticed on pregnant rats when exposed to formaldehyde and gasoline (12). Two anencephalic cases of human birth defects were reported in formaldehyde-contaminated homes (13). Also formaldehyde produced incomplete axial rotation and delayed neural tube closure in mice (14). The embryotoxic and teratogenic effect of formaldehyde in chick embryos were noticed to include cranial hematomas, facial abnormalities, eye and beak deformities (15). There were

no related signs of developmental toxicity in pregnant rats when they administrated formaldehyde orally, as well as among pregnant hamsters when treated by topical application of formaldehyde (16,17).

From the above introduction the present study was designed to examine possible teratogenic effect of formaldehyde on newborn rabbits.

Materials and methods

Thirty three adult female rabbits were used, their weight ranged between 1085-1622 g and they were kept under the same environmental conditions. The animals were kept in stainless steel mesh cages,the temperature was maintained at 22-27 ^{o}C, a dry, absorbent, bedding materials, like wood shaving were provided in all cages. All animals were allowed free access to food and water. An anthelmintic drug (ivermectin 2 mg/kg subcutaneous) was also given as a measure against internal and external parasites. All the animals were observed for 10 days before the beginning of the experiment to exclude any possibility of abnormal behavior and disease.

Female rabbits were mated with males and then randomly assigned irrespective of age and weight into the following groups:

1- Exposed group which included 26 pregnant rabbits.
2- Control group which included 7 pregnant rabbits.

All the females of exposed group (2-3 animals were housed in one separate cage),were exposed to the vapour of 10% formaldehyde during the entire gestation period. The 10% formaldehyde solution was placed in 400- steel containers which is covered by nylon mesh and filled periodically. All the animals were exposed to the same constant surface area of 10% formalin solution.

Analytic procedure (18) was applied several times during the exposed period of this work to determine the concentration of formaldehyde (ppm) in the atmosphere of the exposed cages. From this analytic measurement the concentration of formaldehyde in the exposed cages was (12 ppm).

While the pregnant rabbits of the control group were exposed to a vapor of distilled water, under the same condition of housing, feeding and duration of the exposure (entire gestation period).

Results

There was no abortion or fetal mortality among the exposed and control pregnant rabbits along all gestation period.

One hundred forty six and thirty eight newborns were obtained from the exposed and control pregnant rabbits respectively.

Fifty two (35.6 %) of newborns showed small for date (19.85 ± 2.76 g) (Figure 1) when compared with the control newborns (38.62 ± 3.35 g), while the other ninety four (64.4 %) newborns showed significant decrease of body weight (32.57 ± 3.18 g).

The most common anomalies seen were:

1- Meromelia (6.8%) (Figure.2).
2- Encephalocele (6.1%) (Figure.3).
3- Oligodactyly (4.1%) (Figure.4).
4- Umbilical hernia (3.4%) (Figure.5).
5- Short tail (3.4%) (Figure.6).

From this (23.8%) anomalies, (13.6%) were seen among the small for date and (10.2%) from the other newborns.

In some cases there was a combination between two anomalies such as meromelia with short tail (2%) and meromelia with encephalocele (1.3%).

Figure (1): Showing the small for date (left) and normal (right) newborns.

Figure (2): Showing the meromelia (arrow).

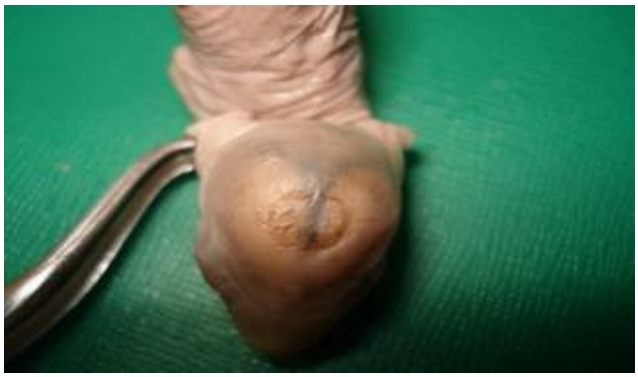

Figure (3): Showing the encephalocele.

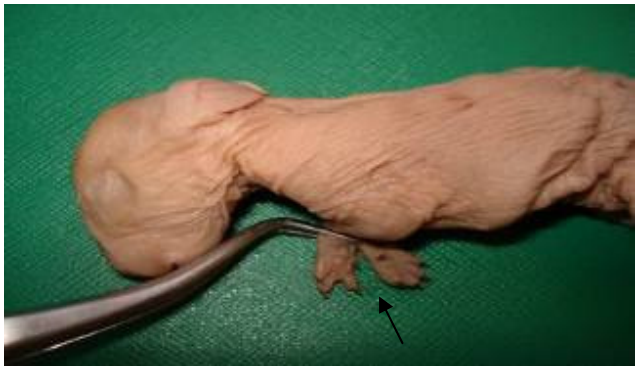

Figure (4): Showing the oligodactyly (arrow).

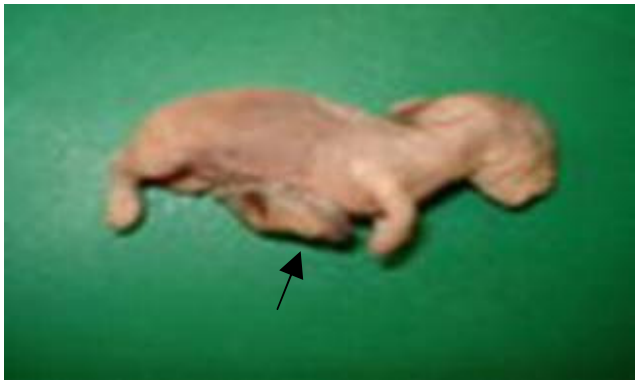

Figure (5): Showing the umbilical hernia (arrow).

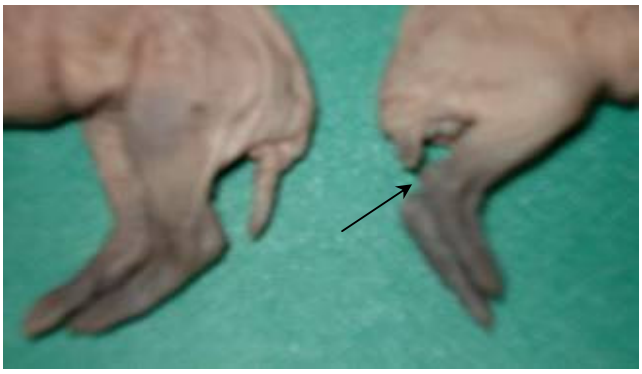

Figure (6): Showing the short tail (arrow).

Discussion

Elimination of formaldehyde and its metabolites from fetal tissues is slower than maternal tissues. It has adverse effects on embryos which showed cytological injury and high rate of mortality, and its exposure throughout gestation caused a decreased DNA and RNA concentrations (19).

Formaldehyde is an alkylating agent and treatment with such an agent has caused primordial germ cell mutations which resulted in fetal deaths and malformations (20); it undergoes addition (adducts and alkylation) and condensation (methene bridges) reactions with proteins and amino acids as well as nucleic acids and nucleosides/tides, so it is regarded as a mutagen, crosslinking agent and an immunogen (21).

Formaldehyde is metabolized to formate. Alcohols, particularly methanol and ethanol, are metabolized to formate and lactate via an aldehyde. The toxicity of alcohols and formalin in humans and animals includes metabolic acidosis (22,23). Alcohol toxicity generates free radicals, cause an increase in malondialdehyde, and induce lipid peroxidation resulting in DNA single strand breaks (24,25). Formaldehyde and alcohols probably affect embryos and the fetus via mitochondrial damage. Ethanol and environmental agents trigger apoptotic neurodegeneration in the developing brain (26). Oxygen stress, such as that caused by free radical generation, is associated with apoptotic cell death and fragmentation of mitochondrial genome (27). Moreover, formaldehyde via formaldehyde generators, e.g. alkylating agents, initiates apoptosis (28) and mitochondria are the suicide organelles which control it (29).

In view of the present finding and its interpretation, we can conclude that formaldehyde has a teratogenic effect (23.8%) of newborn of pregnant rabbits at concentration of (12 ppm). This effect is affected with different factors such as the concentration of formaldehyde, time exposure, rout of administration, material subject, individual variation (human or animal), order or species of animal.

References

1. Occupational Safety and Health Administration (OSHA) Occupational exposure to formaldehyde.1995; OSHA Fact Sheet, Jan 1.
2. National Institute for Occupational safety and Health(NIOSH) Formaldehyde.1996; CAS Number 5000. IDLH Documentation.
3. Feinman SE. Exposure to Formaldehyde. In: Formaldehyde Sensitivity and Toxicity. CRC Press:Boca Raton. 1988; pp. 17-36.
4. AL-Saraj A, AL-Hubaity A. Histological and histopathological changes of lung of rats during different periods of formaldehyde exposure. Iraqi J. Vet. Sci.2003; 17(2):111-21.
5. Occupational Safety and Health Administration (OSHA): Formaldehyde fact sheet. 2002;U.S. Department of labor.
6. Collins JJ, Lineker GA. A review and meta-analysis of formaldehyde exposure and leukemia. Regul Toxicol Pharmacol.2004; 40(2):81-91.
7. Fujimaki H, Kurokawa Y, Kunugita N, Kikuchi M, Sato F, Arashidani K. Differential immunogenic and neurogenic inflammatory responses in an allergic mouse model exposed to low levels of formaldehyde. Toxicology.2004; 1; 197(1):1-13.
8. U.S.Environmental Protection Agency (USEPA): Formaldehyde. EPA Health Effects Notebook for Hazardous Air Pollutants. Office of Air Quality Planning and Standard.1997; Cas. No. 50-00-0.
9. U.S. Environmental Protection Agency(USEPA): Health and Environmental Effects Profile of Formaldehyde. Environmental Criteria and Assessment Office. Cincinnati, OH.1988; EPA/600/x-85/362.
10. World Health Organization (WHO). Environmental Health Criteria for Formaldehyde.1989; Vol. 89. World Health Organization, Geneva, Switzerland.
11. Senichenkova IN, Chebotar NA. The effects of gasoline and formaldehyde on the prenatal Development of rats with induced iron trace-element disorder. Ontogenz.1996; 27, pp.108-13.
12. Senichenkova IN. The embryotoxic effect of industrial environmental pollutants: Formaldehyde and Gasoline. Gig Sanit. 1991; 9,pp.35-38.
13. Woodbury MA, Zenz C. Formaldehyde in the home environment: Prenatal and infant exposures. In: Formaldehyde Toxicity (Gibson JE, ed.) Hemisphere Publishing Corp:New York, 1983; pp.203-211.
14. Hansen JM, Contreras KM, Harris C. Methanol, formaldehyde, and sodium formate exposure in rat and mous conceptuses: a potential role of the visceral yolk sac in embryotoxicity. Birth Defects Res A Clin Mol Teratol. 2005; Feb;73,2,pp.72-82.
15. Friedberg BH, Gartner LP : Embryotoxicity and teratogenicity of formocresol on developing chick embryos. J End.1990; Sep;16,9,pp.434-7.
16. Itami T, Ema M, Kawasaki H. : Teratogenic evaluation of p-tert-butylphenol formaldehyde resin (novolak type) in rats following oral exposure. Drug Chem Toxicol.1993;16,4,pp.369-82.
17. Overman DO. Absence of embryotoxic effects of formaldehyde after percutaneous exposure in hamsters. Toxicol Lett.1985; Jan;24,1,pp.107-10.
18. Hoogenboom M, Hynes R, Mann C, Ekman M, Mcjilten C, Steven J Validation of a colorimetric method for determination of atmospheric formaldehyde. Am.Ind.Hyg.Assoc.J.1987; 48,5,pp.420-424.
19. Thrasher JD, Kiburn KH Embryotoxicity and teratogenicity of formaldehyde.Arch Environ Health. 2001;56,4,pp.300-11.
20. Generoso WM, Shourbaji AG, Piegorsch WW, Bishop JB. Developmental response of zygotes exposed to similar mutagens. Mut Res. 1991;250,pp.439-446.
21. Speit G, Schultz P, Merk O. Induction and repair of formaldehyde-induced DNA-protein crosslinks in repair-deficient human cell lines. Mutagenesis. 2000; 15,pp.85-90.
22. Tephly TR.The toxicity of methanol. Life Sci.1991;48,pp.1031-1034.
23. Pandey CK, Agarwal A, Baronia A, Singh N Toxicity of formalin and its management. Hum Exper Toxicol.2000; 19,pp.330-366.
24. Kadiiska MB, Mason RP Acute methanol intoxication generates free radicals in rats: ESR spin trapping investigation. Free Radic Biol Med.2000; 287,pp.1106-1114.
25. Navasumrit P, Ward TH, Dodd NJ, O'Connor PJ. Ethanol-induced free radicals and hepatic DNA strand breaks are prevented in vivo by antioxidants: effects of acute and chronic ethanol exposure. Carcinogenesis.2000; 21,pp.93-99.
26. Ikonomidou C, Bittigau P, Ishimuaru, MJ, Wozniak DF. Ethanol-induced apoptotic neurodegeneration and fetal alcohol syndrome. Science.2000; 287,pp.1056-1060.
27. Yoneda M, Katsumata K, Hayakawa M. Oxygen stress induces apoptotic cell death associated with fragmentation of mitochondrial genome. Biochem Biophys Res Comm.1995; 209,pp.723-729.
28. Szende B, Tyihak E, Trezly L. Formaldehyde generators and capturers as influencing factors of mitotic and apoptotic processes. Acta Biol Hung.1998; 49, pp.323-329.
29. Ferri KG, Kroemer G. Mitochondria – the suicide organelles. Bioessays. 2001;23,pp.111-115.