Journal of Clinical Toxicology
ISSN: 2161-0495

Wang et al., J Clin Toxicol 2016, 6:2
DOI: 10.4172/2161-0495.1000291

Short communication Open Access

Two Generation Reproduction and Teratogenicity Studies of Feeding Diaveridine in Wistar Rats

Xu Wang[1], Xianglian Liu[2], Shijia Su[2], Ihsan Awais[3], Qianying Liu[2], Dongmei Chen[2], Zhenli Liu[4], Yulian Wang[4*] and Zonghui Yuan[1,2,4*]

[1]National Reference Laboratory of Veterinary Drug Residues (HZAU) and MAO Key Laboratory for Detection of Veterinary Drug Residues, China

[2]MOA Laboratory for Risk Assessment of Quality and Safety of Livestock and Poultry Products, Huazhong Agricultural University, Wuhan, Hubei, 430070, China

[3]Department of Biosciences, COMSATS Institute of Information Technology, Sahiwal, Pakistan

[4]Hubei Collaborative Innovation Center for Animal Nutrition and Feed Safety, Wuhan, Hubei, China

[*]Corresponding authors: Yulian Wang, Hubei Collaborative Innovation Center for Animal Nutrition and Feed Safety, Wuhan, Hubei, China, E-mail: wangyulian@mail.hzau.edu.cn

Dr. Zong-hui Yuan, National Reference Laboratory of Veterinary Drug Residues (HZAU) and MAO Key Laboratory for Detection of Veterinary Drug Residues, China, Tel: 0086-27-87287186; Fax: 0086-27-87672232; E-mail: yuan5802@mail.hzau.edu.cn

Received date: January 6, 2016; **Accepted date:** April 6, 2016; **Published date:** April 13, 2016

Short Communication

Diaminopyrimidines are usually in combination with sulfonamides to improve efficiency of bacterial inhibition or killing, and also known as dihydrofolate reductase (DHFR) inhibitors to impede the synthesis of folic acid [1-3]. Folic acid is important for normal development of the fetus and placenta [4]. Folic acid deficiency on pregnant rats might result in depressed feed consumption and produced smaller sized litters with lower birth weights and poor survival rate [5]. Baquiloprim (BQP), trimethoprim (TMP), ormetoprim (OMP), aditoprim (ADP) and diaveridine (DVD) work as DHFR inhibitors, suggesting that they might result in reproductive and developmental toxicity to females. In recent years, this kind of medicine has been paid more and more attention in terms of metabolism and toxicity [6-9]. It was reported that Baquiloprim (BQP) had the serious maternal toxicity and resulted in cleft palate [10]. TMP was reported to increase the risk of certain birth defects in infants [11,12]. Another study showed that TMP was also found to be responsible for fetal malformations in rats at 300 mg/kg b.w. [13,14]. DVD has been used in food production for many years, but the toxic characteristics of DVD on the reproduction and development still remain unknown.

By two generation reproduction and teratogenicity studies to detect the reproductive toxicity and teratogenic potential of DVD, the results showed that body weights, feed efficiency, weight gain of pregnant rats, the litter and the average number of live fetus and fetus body weight were significantly decreased in 1150 and 2000 mg/kg groups. It was presumed that a constant exposure of DVD to F0 and F1 females induced a worse maternal toxicity in high dose groups, which resulted in worse developmental conditions in their pups. In the reproductive and teratogenic study for ADP, at 1000 mg/kg ADP diet group, body weights, fetal body weight after birth and number of viable fetuses significantly decreased when compared with control group [9]. Moreover, uterine wall contraction, uterine cavity narrow and uterine tumors were observed in 2000 mg/kg group. In 1150 and 2000 mg/kg groups, litter weights, body weights, body length, tail length of fetus and number of viable fetuses were significantly decreased. It indicated that high dose exposure of DVD could induce the developmental inhibition on pups in both generations. In addition, there were no obvious external, skeletal and visceral effects in all groups. There were no toxicological signs observed for teratogenicity test in female SD rats at the dosage of 37 mg/kg DVD body weight [7].

In the present study, the two-generation reproductive toxicity study and teratogenic test were firstly performed to further evaluate the potential effects of DVD on reproduction and development of rats, which provided the information about adverse effects of DVD on parents and their developing fetuses. Previous studies have found that DVD had genetoxicity that DVD induced structural chromosome aberrations and DNA damage in liver, kidney, lung, and spleen cells [15,16]. In Ames test, DVD was mutagenic in strain TA100 after metabolic activation with hamster S9 mix [16]. However, the testing results for three terms of mutagenicity including mouse chromosome aberration, erythrocyte micronucleus and sperm abnormality were all negative at 128~512 mg/kg DVD diet group [7]. Accordingly, DVD is safe to a certain extent, and DVD has genetoxicity once more than a certain dose. But these are also insufficient to evaluate the toxicity of DVD according to the relative toxicology guidelines. Thus the experiments of reproductive and developmental toxicity studies of DVD provide scientific information for further risk evaluation of DVD in food animals.

In summary, high dose level of 2000 mg/kg DVD (about 213.5~262.9 mg/kg b.w/day) depressed the development of the fetus and fertility of rats. For a long-term perspective, it is of great significance for the safety assessment of DVD, especially because of the concerns related to the potential impact on human health of the proposed use in food producing animals.

Conflict of interest statement

The authors declare that there are no conflicts of interest.

References

1. Capasso C, Supuran CT (2014) Sulfa and trimethoprim-like drugs - antimetabolites acting as carbonic anhydrase, dihydropteroate synthase and dihydrofolate reductase inhibitors. J Enzyme Inhib Med Chem 29: 379-387.
2. Hawser S, Lociuro S, Islam K (2006) Dihydrofolate reductase inhibitors as antibacterial agents. Biochem Pharmacol 71: 941-948.
3. Tosso RD, Andujar SA, Gutierrez L, Angelina E, Rodriguez R, et al. (2013) Molecular modeling study of dihydrofolate reductase inhibitors. Molecular dynamics simulations, quantum mechanical calculations, and experimental corroboration. J Chem Inf Model 53: 2018-2032.
4. Scholl TO, Johnson WG (2000) Folic acid: influence on the outcome of pregnancy. Am J Clin Nutr 71: 1295S-303S.

5. Tagbo IF, Hill DC (1977) Effect of folic acid deficiency on pregnant rats and their offspring. Can J Physiol Pharmacol 55: 427-433.
6. Wang H, Yuan B, Zeng Z, He L, Ding H, et al. (2014) Identification and elucidation of the structure of in vivo metabolites of diaveridine in chicken. J Chromatogr B Analyt Technol Biomed Life Sci 965: 91-99.
7. Wang J, Sun F, Tang S, Zhang S, Cao X (2015) Acute, mutagenicity, teratogenicity and subchronic oral toxicity studies of diaveridine in rodents. Environ Toxicol Pharmacol 40: 660-670.
8. Wang L, Huang L, Pan Y, Kuca K, Klimova B, et al. (2016) Metabolism and Disposition of Aditoprim in Swine, Broilers, Carp and Rats. Sci Rep 6: 20370.
9. Wang X, Tan Z, Cheng G, Awais I, Huang L, et al. (2015) Two-generation reproduction and teratology studies of feeding aditoprim in Wistar rats. J Appl Toxicol 35: 1531-1538.
10. EMEA (1997b) Baquiloprim. Summary Report (2) (EMEA/MRL/199/97-FINAL), London, UK, European Agency for the Evaluation of Medicinal Products.
11. EMEA (1997a) Trimethoprim. Summary Report (2) (EMEA/MRL/255/97-FINAL), London, UK, European Agency for the Evaluation of Medicinal Products.
12. Hernández-Díaz S, Werler MM, Walker AM, Mitchell AA (2000) Folic acid antagonists during pregnancy and the risk of birth defects. N Engl J Med 343: 1608-1614.
13. Bushby SR, Hitchings GH (1968) Trimethoprim, a sulphonamide potentiator. Br J Pharmacol Chemother 33: 72-90.
14. Thiersch J (1963) The effect of substituted 2,4-diaminopyrimidines on the rat fetus in utero. 3rd International Congress of Chemotherapy, International Society of Chemotherapy, Stuttgart, Germany. 367-372.
15. Ono T, Sekiya T, Takahashi Y, Sasaki YF, Izumiyama F, et al. (1997) The genotoxicity of diaveridine and trimethoprim. Environ Toxicol Pharmacol 3: 297-306.
16. Yoshimura H (1991) Mutagenicity of the coccidiostat diaveridine in the Salmonella/mammalian microsome assay. Mutat Res 261: 149-152.