

## Effect of Erythromycin on Albendazole-Induced Teratogenicity in Pregnant Rats

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Article information	Abstract
<p>Article history: Received: 1 June 2012 Accepted: 24 Oct 2012 Available online: 18 Nov 2012 ZJRMS 2013; 15(5): 43-46</p> <p>Keywords: Albendazole Erythromycin Teratogenicity Rats</p> <p>*Corresponding author at: Department of Pharmacology, Department of Basic Sciences, Faculty of Veterinary Medicine, Shahid Chamram University, Ahwaz, Iran. E-mail: najafzadeh@scu.ac.ir</p>	<p><b>Background:</b> Albendazole is utilized as an anthelmintic agent. One its side effect is teratogenicity. This effect apparently is related to its metabolites especially albendazole sulfoxid. The aim of present study was evaluation effect of erythromycin (as enzyme inhibitor in biotransformation) on albendazole biotransformation and consequently fetal malformation.</p> <p><b>Materials and Methods:</b> Four groups of female pregnant wistar rats (8 rats each group) were used. First group received normal saline (as control group). A single oral dose 30 mg/kg of albendazole was administered to rats on day 10 of gestation in group 2. Rats in group 3 received albendazole similar group 2 and erythromycin at dose 60 mg/kg. Rats in group 4 received only erythromycin on day 10 of gestation. The rats were euthanatized on day 20 of gestation. The skeletal malformation of fetus was studied by stereomicroscope after staining by Alizarin red-Alcian blue.</p> <p><b>Results:</b> The length and weight of fetuses were significantly decreased by albendazole but erythromycin did not prevent this effect. In group that received only erythromycin, the length and weight of fetuses was similar to control group. Erythromycin decreased albendazole effect on weight of placenta. There was an increase in resorption by erythromycin when co-administrated with albendazole. The incidence of skeletal malformations (mostly of the limbs, vertebrae and palate) decreased significantly by erythromycin when co-administrated with albendazole.</p> <p><b>Conclusion:</b> Thus, erythromycin may inhibit albendazole biotransformation and decrease teratogenicity of it metabolites; but this subject needs more detailed evaluation.</p> <p>Copyright © 2013 Zahedan University of Medical Sciences. All rights reserved.</p>

### Introduction

Albendazole is broad spectrum anthelmintic and affects nematodes, cestodes and trematodes. This drug belongs to benzimidazole group which act by binding to parasite-tubulin, inhibiting its polymerization and impairing glucose uptake and carbohydrate metabolism in parasites and cause their death [1]. Albendazole is choice for treatment of microsporidiosis, ascariasis, enterobiasis, hookworm infections, cystic hydatid disease and neurocysticercosis [2]. Albendazole is safe in human and animals. The incidence of its side effects is very low; with gastrointestinal side effects (lesser than 1%) [3] and teratogenic effect especially in laboratory animals such as rat. Albendazole is initially oxidized to albendazole sulphoxide, an active metabolite, and then to albendazole sulphone, which is inactive [4].

Its metabolism is induced or inhibited by the cytochrome P450 system inducer such as phenobarbital or inhibitor including erythromycin. Albendazole sulphoxide is 70% protein bound and has a half-life of 9 h [2]. Erythromycin is a broad spectrum macrolide antibiotic. Erythromycin has the potential to interact with many drugs by inhibiting drug metabolism in the liver [5]. It is

used for treatment of respiratory tract infections, chlamydial and other genital tract infections in pregnancy, puerperal mastitis, and acute conjunctivitis of the newborn [6]. The available data does not indicate that use of erythromycin is associated with an increased risk of skeletal malformations [7, 8].

The objective of the present study was to evaluate interaction between erythromycin and albendazole and effect of erythromycin on weight, length and skeletal malformation in rat fetuses, caused by the administration of albendazole during pregnancy. This interaction was not evaluated previously and this experimental study is important in teratology.

### Materials and Methods

This experimental study was done in animal model in department of basic sciences of faculty of veterinary medicine of Shahid Chamram University (Ahwaz, Iran). Male and female healthy Wistar rats, 10-12 weeks of age, weighing 180-200 g were purchased (Joundishapour laboratory animal center, Ahwaz, Iran) and housed individually (males) or at 10 per polycarbonate cage

(female) for a 2-week acclimation period. Rats were fed ad libitum by standard laboratory pellet (Pars Khurakdam, Shushtar, Iran.) and tap water. A 12-h light: 12-h dark cycle was maintained. Room temperature was at  $23\pm 2^{\circ}\text{C}$  with a relative humidity of 45-55%. The animal care was provided under the supervision of a qualified veterinarian.

Male and female rats were housed together. Pregnant females were divided into four groups (N=8) and treated as follow on pregnant day 10: First group received normal saline (10 ml/kg), the second group received albendazole (30 mg/kg) orally, the third group received albendazole (30 mg/kg) and along with it erythromycin esteolate (60 mg/kg) intraperitoneally, and the fourth group received erythromycin (60 mg/kg). Albendazole and erythromycin was purchased from Sigma Co., USA.

The animals were sacrificed by cervical dislocation at 20th day of gestation and fetuses were collected and numbered, then weight and length of them were measured and gross malformations were determined. The weight of placenta was measured. Fetuses were stained by Alizarin red-Alcian blue method [9] and investigated by stereomicroscope (Nikon, Japan) for skeletal defects. The incidence of macroscopic defects was determined and was compared in the groups.

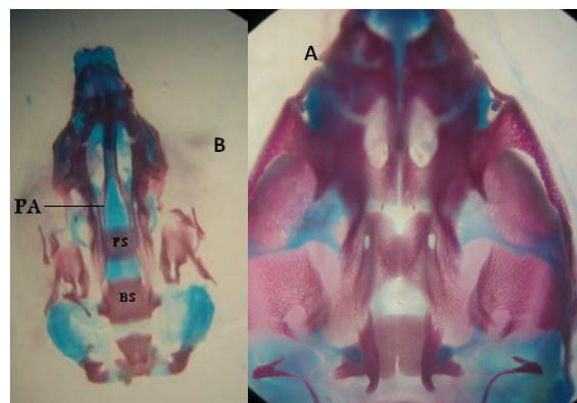
Statistical significance between groups was determined using SPSS-16 program. Significance of differences between groups were assessed using one-way analysis of variance (ANOVA) followed by least significant difference post hoc comparison. The minimum level of significance was  $p < 0.05$ .

## Results

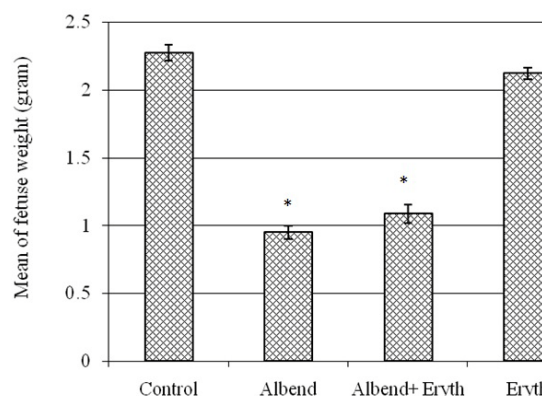
There were not any aborted or absorbed fetuses from normal saline group. Total number of collected fetuses from groups 1, 2, 3 and 4 were 26, 64, 44 and 29, respectively. There were not observed macroscopic anomalies in the control animals. In the control group palatal closures of fetuses were normal at gestational day 20 (i.e., palatal shelves had grown vertically on the sides of the tongue, then horizontally to meet and fuse) (Fig. 1A). Albendazole induced cleft palate at 46% incidence (Fig. 1B). Erythromycin reduced incidence of albendazole-induced cleft palate to 35%. Percentages of absorbed fetuses were 39.2, 22.8 and 23.3 in groups 2 to 4, respectively. Double ossification center in vertebral column was observed by albendazole (23% of fetuses in group 2). Its incidence was decreased by erythromycin (14.7% of fetuses in group 3).

Mean weight and length (CRL) were significantly decreased in the group which received only albendazole ( $p < 0.05$ ). The means of weight and length of fetuses in the group that received albendazole along with erythromycin were not significantly greater than the group received only albendazole. The mean weight and length in the group that received erythromycin did not significantly differ with control group (Fig. 2, 3) ( $p < 0.05$ ). The means of weight of placenta in the group that received albendazole along with erythromycin was

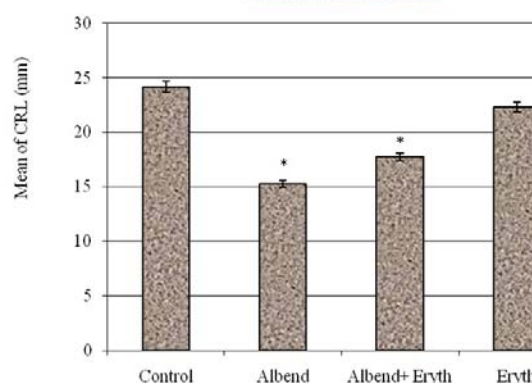
significantly greater than the group received only albendazole. This mean in the group that received erythromycin did not significantly differ with control group (Fig. 4).



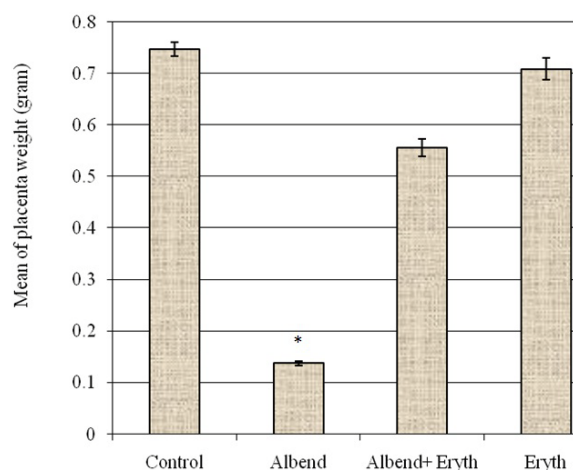
**Figure 1.** Ventral view of skull of GD 20 fetal rats. A: Normal palatine bone B: Cleft palate induced by albendazole which stained with Alizarine red- Alcian blue. PS: palatine; BS: sphenoid



**Figure 2.** Weight (Mean $\pm$ SD) of fetuses in normal saline and test groups: 1: normal saline (control) (1 ml/100g IP); 2: albendazole (30 mg/kg po); 3: albendazole+erythromycin (60 mg/kg IP); 4: erythromycin (60 mg/kg IP). N=8. \* shows significant difference with control and erythromycin groups ( $p < 0.05$ )



**Figure 3.** Length (CRL) (Mean $\pm$ SD) of fetuses in normal saline and test groups: 1: normal saline (control) (1 ml/100g IP); 2: albendazole (30 mg/kg po); 3: albendazole+erythromycin (60 mg/kg IP); 4: erythromycin (60 mg/kg IP). N=8. \* shows significant difference with control and erythromycin groups ( $p < 0.05$ )



**Figure 4.** Weight (Mean±SD) of placenta in normal saline and test groups: 1: normal saline (control) (1 ml/100g IP); 2: albendazole (30 mg/kg po); 3: albendazole+erythromycin (60 mg/kg IP); 4: erythromycin (60 mg/kg IP). N=8. \* shows significant difference with other groups ( $p<0.05$ )

## Discussion

Pregnant rats were received 30 mg/kg of albendazole on gestational days 10. This dose of albendazole was toxic for embryos. Some embryos were absorbed and some had growth reduction which characterized by reduced fetus body weight and placental weight (Fig.2 and 4). The growth reduction was very considerable, so the fetuses were seen immature on day 20 of pregnancy. The mean of fetus length in group 2 was significantly lesser than control group. Similar effect of albendazole was reported in several studies. Embryo lethality and growth reduction was reported by Mantovani et al. They seen this effect was dose dependent. At 20 and 30 mg/kg, more than 20% of embryos showed morphologic alterations including shape abnormalities and the development of forelimb buds [10].

Albendazole affected ossification process in fetuses. In our study, the skeletal malformation was included cleft palate (in 46% fetuses) and double ossification center in vertebral column (in 23% fetuses). In addition, albendazole directly acts on the embryogenesis causes malformations, like agenesis of the tail and hydropic fetuses [11]. The incidence of external and skeletal malformations (mostly of the tail, vertebrae and ribs, gross external and skeletal abnormalities in the thoracic region and limbs) was reported with albendazole sulphoxide [12].

It appears the embryo toxicity and teratogenicity of albendazole relates its major active metabolite as known albendazole sulfoxide. Albendazole is normally not detectable in human plasma since it is rapidly metabolized

[4]. Both albendazole and its sulfoxide metabolite produce embryotoxic effects in this rat model [13].

Data of resorptions, placental and fetal characteristics and fetal skeletal malformations by albendazole sulfoxide were recorded. Resorption and decreasing of Placenta weight and smaller size fetuses by albendazole sulfoxide was reported by Teruel et al. Also they observed reductions in ossification process and malformations or fetal death when albendazole sulfoxide was orally administered to pregnant rats [14].

We administrated erythromycin with albendazole by this thought the hepatic metabolism of albendazole was reduced with erythromycin. Thus the rate of albendazole sulfoxide production was decreased. Consequently, its embryo toxicity and teratogenic effect may reduce. Co-administration of erythromycin prevented effect of albendazole on placenta weight. Also, it decreased albendazole-induced skeletal malformation such as cleft palate and vertebrate ossification. Although, no teratogenic effect has been recorded for erythromycin [7, 15]; and erythromycin (except erythromycin estolate is hepatotoxic for mother) can be safe for the fetus and for the pregnant woman [8]. However, erythromycin crosses the placenta but its concentration is very low [16]. The risk for any congenital malformation after erythromycin therapy was increased and this was due to an effect on cardiovascular malformations. Also it was reported an increased risk for pyloric stenosis of fetuses by erythromycin after exposure in early pregnancy [17]. Erythromycin caused prolongation of pregnancy period and increased live birth weight in LPS-induced preterm labor of pregnant rats [18]. We demonstrated that the erythromycin had embryo toxicity because it caused absorption in 23.3% of fetuses, but no skeletal malformation was seen by erythromycin.

In summary, with present experimental study we demonstrated the erythromycin as drug metabolism inhibitor can decrease some teratogenic effect of albendazole. Although, we proposed another safe biotransformation inhibitor and dosage is evaluated.

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## Authors' Contributions

All authors had equal role in design, work, statistical analysis and manuscript writing.

## Conflict of Interest

The authors declare no conflict of interest.

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