EXPERIMENTAL DATA REGARDING THE EFFECTS OF AMIODARONE IN PREGNANT RATS

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ABSTRACT: The present study was designed to evaluate the effects of amiodarone, an antianginal and antiarrhythmic agent on pregnant rats. The drug was administered at dosages of 10 mg/kg/day and 90 mg/kg/day, intaperitoneally, once, to the pregnant female rats (on the 10th and the 12th day of gestation). Clinical signs, body weight and feed consumption were recorded daily. Evaluations were made for number of newborn cubs and number of cubs born dead, number of cubs born with malformations and number of cubs dead after birth (during the first 30 days); cubs were also examined for body weight. An increased frequency of deaths amongst newborn cubs and a decrease in their body weights were observed in rats to which doses of 90 mg/kg/day were administered. In the same way, it has been shown that the offspring nursing by lactating rats, treated during gestation with amiodarone, were less viable and have gained reduced body-weight.

KEY WORDS: Amiodarone; Embriogenesis; Malformations.

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INTRODUCTION

Amiodarone is a benzofuran derivative, a member of a new class of antiarrhythmic drugs with predominantly class III (Vaughan Williams' classification) effects. In animals, amiodarone is effective in the prevention or suppression of experimentally induced arrhythmia. The antiarrhythmic effect of amiodarone may be due to at least two major properties: 1) a prolongation of the myocardial cell-action potential duration and refractory period and 2) a noncompetitive alpha- and beta- adrenergic inhibition.

Beside the antiarrhytmic properties, amiodarone is also an effective antianginal drug, acting both through coronary and systemic vasodilatation, as well as by decreasing myocardial oxygen consumption.

With all these properties, amiodarone is intended for use only for patients in whom life-threatening arrhythmia is indicated because its use is accompanied by substantial toxicity; it has several potentially fatal toxic actions, the most important of which is pulmonary toxicity.

The aim of the present study was to evaluate the effects of amiodarone in pregnant rats, because amiodarone is a drug that passes trough the placental barrier.

STUDY DESIGN

We studied the consequences of amiodarone administration during embriogenesis in the pregnant female rats, amiodarone being administered intraperitoneally, once on the 10th, and once on the 12th day of gestation.

All experiments were performed on white female adults rats weighing 180 ± 20 g, maintained in the same environmental conditions (20–22°C temperature, light cycle (12 h) and humidity (55%)) and subjected to the same elementary diet; tap water were provided ad libitum.

The rats were divided into groups made up of 20 animals:

- group number I – control group (with animals that didn't receive any treatment),
- group number II – the rats were treated with 10 mg/kg bw amiodarone,
- group number III – including rats treated with 90 mg/kg b.w. amiodarone.

The studied parameters of all groups were:

- the gestational period,
- the size of conception/litter,
- the number of alive new born cubs,
- the new born mortality,
- the weight of the new born,
- the percentage of cubs surviving during the first 30 days,
- the number of cubs born with malformations,
- the maternal mortality (%),
- the maternal weight during lactation.

RESULTS AND DISCUSSIONS

Pregnancy is a physiological state which involves pharmacological particularities of a great importance, which can be recorded in well to the embryo, as to the cub or to the mother. These pharmacological particularities can also have an influence over on labor.

The majority of drugs are lipophiles and, having a relatively low molecular weight they are able to cross the placenta through diffusion and hence act directly on the embryo and the fetus. Medicinal substances can interfere with the intrauterine development leading to different adverse reaction which affect directly the fetus (fetal death, development defects visible at birth) or which will appear in later.

Amiodarone is one of the drugs that could be administered during pregnancy, even so it should only be administered quite rarely, namely when there is a potentially beneficial effect on the mother that justifies the unknowns effects on the fetus.

The present investigation was conducted to study the consequences of amiodarone administration during pregnancy as well as its teratogenic potential, because amiodarone and its major metabolite, desethylamiodarone, have a transplacental transfer of approximately 10 to 50%.

Two doses were used (10 mg/kg body weight and 90 mg/kg body weight) estimated in relation with the maximum therapeutic daily dose in man, being administered in a single dose, intraperitoneally, during pregnancy.

The female rats were mated overnight for 12 hours with male rats at the beginning of the experiment, the zero day of pregnancy being considered as the day of pregnancy.

Clinical signs, body weight and feed consumption were recorded daily in to all animals, but amiodarone did not cause visible clinical signs nor significant body weight changes,not significant changes in food and water consumption in rats at these doses; only at the end of pregnancy did group II and III animals exhibit tremors at some moments.

In what is regarded at as the gestational period significant differences were not observed compared with the control group – the gestational period fitted within normal limits in both groups of animals treated with amiodarone (Figure 1).

Referring to the size of the litter, a marker of the animal's fertility, we found a

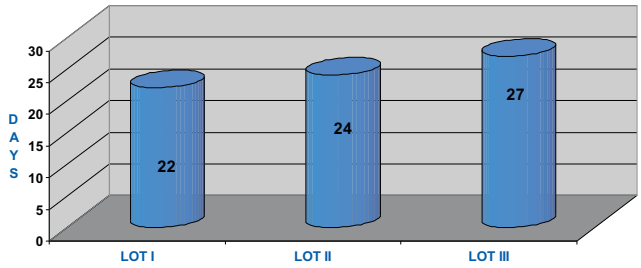

Fig. 1. Duration of gestation.

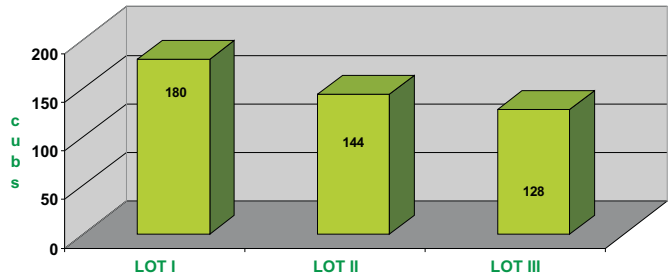

Fig. 2. Size of conception (total number of newborn cubs).

reduction in the total number of the new born, mainly in group III animals (Figure 2).

We also observed a decrease in the viability of the new born cubs (Figure 3), the number of new born cubs born dead being greater in group II and especially group III compared with group I (the control group) (Figure 4). A similar situation was also

recorded with regard to the percentage of surviving cubs during the first 30 days after birth (Figure 6).

The newborns were examined for body weight and gross external, soft tissue and skeletal alterations. No in born malformations or somatic abnormalities were recorded either in group II or in group III; however, reduced birth weights of the new born from

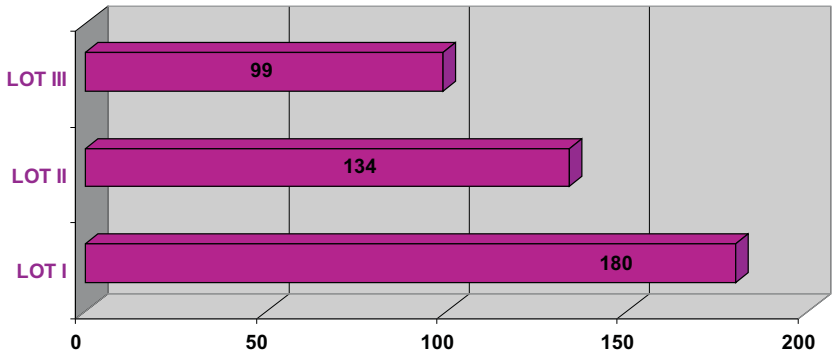

Fig. 3. Number of alive newborn cubs.

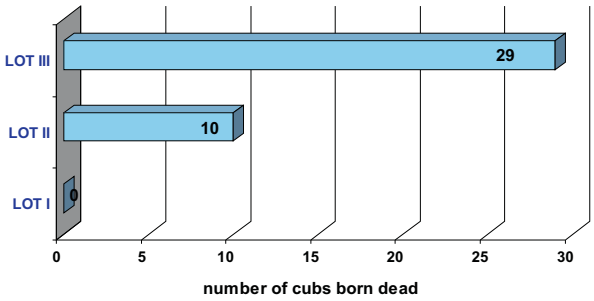

Fig. 4. Newborn cubs mortality.

mothers treated with 90 mg/kg bw/day amiodarone were noted (Figure 5).

The results obtained by us shoved that treating the female rats during pregnancy with 90 mg/kg b.w. also led to maternal toxicity as was showed by the significant rise in maternal mortality (Figure 7) and also by the reduction in maternal body weight during lactation (Figure 8).

CONCLUSIONS

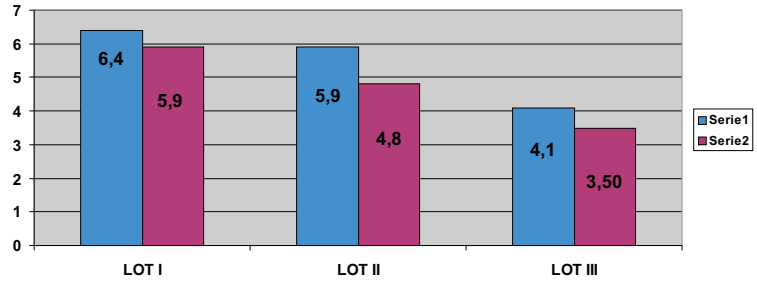

Fig. 5. Newborn cubs weight (g) – medium values.

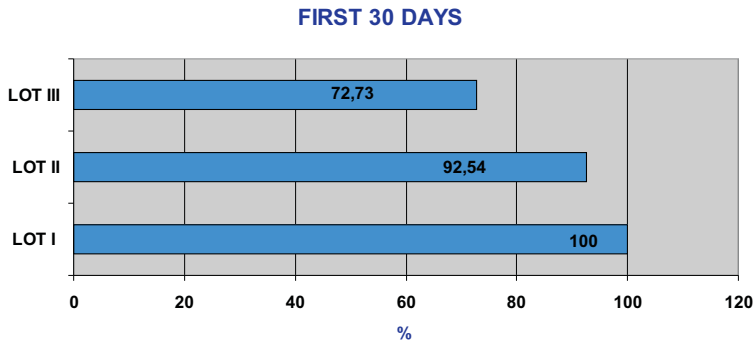

Fig. 6. The percentage of cubs survivals during the first 30 days.

1. Amiodarone administration, in single doses, to pregnant rat's female, during embriogenesis has not generated malformations in newborn and had no effect on gestational period.
2. Administration of 90 mg/kg b.w. amiodarone intraperitoneally on the 12th gestational day rised the newborn mortality and lowered their body weight and also led to maternal toxicity.
3. Prescribing amiodarone during pregnancy can be done only if the benefit to the mother justifies the unknown risk to the fetus.

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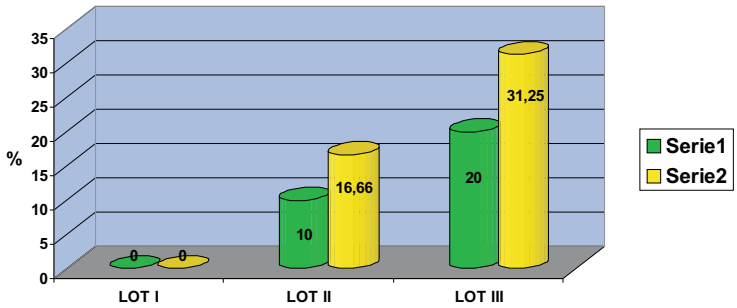

Fig. 7. Maternal mortality [%].

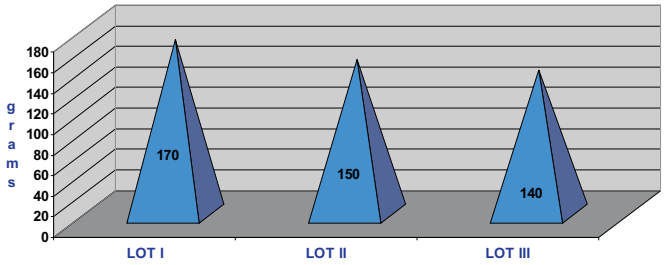

Fig. 8. Maternal weight during lactation [g].

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