Influence of Hypothyroidism Induced by Thiamazole on the Toxic Interaction between Propranolol and Disopyramide in Chick Embryos

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The present study evaluated the effect of the hypothyroidism induced by thiamazole on the toxic interaction between propranolol and disopyramide in chick embryos. Fertilized eggs of White Leghorns were incubated and investigated. 1.2 mg/0.2 ml/egg of thiamazole was injected into the albumen of fertilized eggs on the 9th day of incubation. The control group was given 0.2 ml/egg of physiological saline in the same manner. Propranolol at 0.1 mg/egg and disopyramide at 0.3 mg/egg were injected into the air sac of fertilized eggs on the 16th day of incubation. Electrocardiograms were recorded 0 to 60 min after the injection. After the injection of propranolol and disopyramide into the thiamazole treated eggs, the heart rate was significantly decreased compared with the thiamazole untreated eggs. These findings indicate that hypothyroidism induced by thiamazole has a marked influence on the toxic interaction between propranolol and disopyramide in chick embryos.

Key words  hypothyroidism; thiamazole; toxic interaction; chick embryo; propranolol; disopyramide

MATERIALS AND METHODS

Fertilized eggs of White Leghorns (Omiya Poultry Laboratory, Saitama, Japan) were incubated at 37.5±0.2 °C at a relative humidity of about 65%, turned automatically every hour.

Thiamazole (Chugai Pharmaceutical, Tokyo, Japan), propranolol preparation (Sumitomo Pharmaceutical, Tokyo, Japan) and disopyramide preparation (Chugai Pharmaceutical, Tokyo, Japan) were used for the treatment. 1.2 mg/0.2 ml/egg of thiamazole was injected into the albumen of fertilized eggs on the 9th day of incubation. The control group was given 0.2 ml/egg of physiological saline in the same manner.

Propranolol at 0.1 mg/egg and disopyramide at 0.3 mg/egg and were injected into the air sac of each fertilized egg on the 16th day of incubation.

After the injection of propranolol and disopyramide into the thiamazole treated eggs or the thiamazole untreated eggs, the heart rate values were measured.

Electrocardiograms (ECGs) were recorded 0 to 60 min after drug injection, and heart rate was determined based on R-R intervals. Changes in heart rate were expressed as mean percentage changes in the drug-treated groups compared with the matched control. Four small holes were made at 90-degree intervals on “the equator,” as well as one small hole on “the south pole,” and one small hole on “the north pole” of each fertilized egg using an electric drill, and there were all sealed with paraffin (mp 60 °C). Specially designed needle electrodes were inserted into the appropriate holes of the equator and the south pole. Two needles on the equator were used as a bipolar lead from the embryonic heart, and the needle on the south pole was used as a ground lead. These needles were connected to a memory oscilloscope (VC-11, Nihon Koden Co., Tokyo, Japan). ECGs were recorded as bipolar waves between two needles on a recorder (PowerLab System, ADInstruments Japan Co., Tokyo, Japan) (Fig. 1).

The data were analyzed by one way analysis of variance. If there was a significant difference among the groups, a multiple comparison test was conducted (Tukey’s test). The fiducial limits of the difference were calculated using Bonferroni’s adjustment.
cial limit of 0.05, two-tails, was used as the criterion to determine significance.

RESULTS

The wet and relative weights to body weight in thyroid of the embryos treated with thiamazole were significantly higher than those of the control (saline) group (3.6±0.76% and 0.9±0.25, p<0.05). After the injection of propranolol with disopyramide, the heart rate was significantly decreased compared with those injected with propranolol alone at the thiamazole untreated eggs (Fig. 2). In addition, this toxic interaction between propranolol and disopyramide was more severe at the chick embryos with hypothyroidism induced by thiamazole.
DISCUSSION

We have reported that toxic interactions between antiarrhythmic drugs were demonstrated in chick embryos. The combination with disopyramide modified the pharmacological effects of the propranolol in chick embryos and led to an arrhythmia of the ECGs. Toxic interactions between disopyramide and other antiarrhythmic agents may result in potentially serious adverse reactions, particularly in patients with intraventricular conduction disturbances. The concurrent administration of Class I antiarrhythmic agents and agents that prolong the QT interval, such as fluconazole, is not recommended. An increased risk of cardiotoxicity may be caused by the additive effects on QT prolongation.

The toxicological and pharmacological effects of cardiovascular drugs are usually studied in mammals and the results obtained are extrapolated to humans. Chick embryonic heart develops through a similar process to that in mice, rats and humans, and also has a similar atrioventricular system. Chick embryos have been widely used in pharmacologic and toxicologic experiments for evaluating drug action on the fetus.

And we have also reported that the chick embryonic model of hypothyroidism produced by treatment with thiamazole can be used to examine the pharmacological and toxicological effects of cardiovascular drugs. In the present study, the effect of the hypothyroidism induced by thiamazole on toxic interactions between propranolol and disopyramide was demonstrated in chick embryos. Indeed, the hypothyroidism induced by thiamazole modified the toxic interaction of these drugs in the chick embryos.

The pharmacological and toxicological activities of thiamazole has characteristics in common with that of thiourea. It has been reported that when thiourea derivatives were injected into the albumen of eggs, the time of the injection strongly affected in the body weight and the thyroid gland weight from the 9th to 12th day of incubation. In addition, they showed that a state of hypothyroidism could be produced in chick embryos by injection of these drugs. It is important to determine the suitable period and site for the injection of drugs into fertile eggs. In the present study, we injected thiamazole into the albumen for fertile eggs on the 9th day of incubation.

As thyroid hormone has multiple functions in chick embryos as well as in mammals, further investigation is necessary to clarify the mechanism underlying cardiac function induced by the toxic interaction between propranolol and disopyramide in chick embryonic hypothyroidism.

In conclusion, our in ovo recording system for ECG of chick embryos may be useful for investigating the toxic interactions of cardiovascular drugs. In addition, thiamazole-treated chick embryos may prove to be an alternative animal model with which to examine some drug–drug interactions, including some antiarrhythmic drugs, under certain experimental situations.

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REFERENCES