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Effect of Anthelmintic Drug in Pregnancy

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Abstract ㄴ Pyrantal pamoate's anthelmintic activity is due to its action as a neuromuscular blocking agent. It is generally well tolerated. Transient rises in SGOT levels have been reported in the drug-treated patients. Decreased levels of serum alkaline phosphatase post treatment were found in young dogs. The present study was performed to investigate the possible toxic effects of pyrantal pamoate in pregnant mice progenies. The drug was given in different doses to these mothers in the first, second and third trimester. Serum alkaline phosphatase, SGOT and SGPT of one or two month old offspring were monitored. SGOT levels showed an increase in some doses in one and two month old offspring where alkaline phosphatase showed a decrease in some doses in one and two month old offspring. The latter effct may be due to osteoblastic alkaline phosphatase inhibition. The effect on SGOT levels, however, was difficult to explain, but may be due to a toxic effect on liver cells or cardiac muscles.

Keywords ㄴ A soluble salt pyrantel tartrate, An isoluble salt pyrantel pamoate, Serum alkaline phosphatase, SGOT, SGPT

Pyrantel pamoate as an anthelmintic drug has been indicated for use in *Enterobiasis vermicularis* (pin worms), *Ascaris lumbricoides* (round worms) and *Nectar americans* (hook worms)[1] infestations.

The anthelmintic activity is due to pyrantel's action as a neuromuscular blocking agent. Two compounds in this class have been developed commercially: a soluble salt pyrantel tartrate which is readily absorbed from the intestine; and the insoluble salt pyrantel pamoate which is only partially absorbed[2].

Pyrantel pamoate is generally well tolerated and has an adverse reaction rate of about 20 to 30 percent. These are related to gastrointestinal distress and are usually transient and mild in nature[3]. Transient rises in SGOT have been seen in the treated patients[3].

The study performed by Snow[4] on greyhounds showed no significant changes in SGPT, SGOT and serum cholinesterase in association with drug treatment. However, serum alkaline phosphatase levels in the young dogs were found to be decreased below pre-treatment levels. Pyrantel pamoate has not been found to be teratogenic in animals[5]. However, it has not been studied fully in humans, and more studies in this respect are needed. Therefore, it is not recommended for use in pregnant women unless deemed essential for the welfare of the patient[6].

An investigation into the possibility of pyrantel pamoate having toxic effects in pregnant mice progenies was carried out by monitoring several serum enzymes of one or two month old

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offspring.

EXPERIMENTAL METHODS

Animal use

Two-month old virgin females and adult males NMRI mice weighing 25~30 grams were used. One female and one male were housed together in a private macrolone cage (27×21×14 cm), on sawdust bedding, under food and water *ad libitum*. The colony room was kept on 12 hour light and 12 hour dark lighting cycle and its temperature was controlled at 24±4°C throughout the experiments.

Determination of the lst day of pregnancy

Each female is mixed with one male in one cage for mating. Each female was observed every day in the early morning for a vaginal plug. The lst time the vaginal plug was observed, was considered the lst day of pregnancy. Each mated female was separated individually in a private cage under food and water *ad libitum*.

Trimesters of pregnancy

The gestation period for mice is around 21 days. It was divided into three parts. The first one started from the first day of pregnancy until the seventh day. This period was designated as the first trimester. The second part began from the eighth day of pregnancy until the fourteenth day and was designated as the second trimester. The third part of the gestation period began from the fifteenth day of pregnancy until the twenty-first day and was designated as the third trimester.

Drug used and dosages selection

Pyrantel pamoate (combantrin) was obtained for oral use as suspension (50 mg/ml) from Pfizer Co., New York, U.S.A. The therapeutic oral dose for pyrantel pamoate is 11 mg/kg as the base. The oral LD_{50} for the drug in mice is 200 mg/kg[7]. Pilot experiment was carried out to select the suitable sublethal oral dose which should be used without appearance of harmful effects on the mother and their offspring[8].

It had been noticed that 30 mg/kg of oral pyrantel pamoate suspension as a base has no toxic symptoms or harmful effects on the pregnant mice and their offspring. It is considered the suitable large dose to be used. Therefore, three oral doses of the drug as a base were selected and used. Small dose (10 mg/kg, intermediate dose (20 mg/kg) or large dose (30 mg/kg) for each group of mice during each trimester of pregnancy.

Calculation of the dose

The drug was diluted in normal saline (0.9 %). Since the concentration of the commercial pyrantel pamoate suspension was 50 mg/ml as a base, 0.6 ml, 0.4 ml or 0.2 ml of the suspended drug was diluted in saline solution up to 10 ml to obtain 30 mg, 20 mg, or 10 mg/kg body weight respectively. The control group of mice for each trimester was given normal saline 10 ml/kg.

Administration of the drugs

The lst day of pregnancy was determined by observing the vaginal plug on the NMRI mice as described above. At the beginning of the lst, 2nd or 3rd trimester of pregnancy, four groups, 10 of each, of pregnant mice were used. The lst, 2nd or 3rd group were given orally 10 mg, 20 mg or 30 mg/day/kg body weight or the drug respectively for seven consecutive days. The 4th control group was administered orally, 10 ml/day/kg body weight saline solution for seven consecutive days too. Each group of pregnant animals received at least 6 doses.

Blood Collection

The one and two month old offsprings were killed by decapitation. Two ml of blood was

collected at the decapitation site into heparinised tubes. The plasma was separated and stored at −20°C. The biochemical tests were performed in batches of each trimester.

Biochemical Studies

(1) Glutamate-Oxaloacetate Transaminase(GOT):

For assaying GOT activity, the principles of Doonan *et al.* (1974) were used.

Principle:

1. 2-Oxoglutarate+L-Aspartate⟶L-Glutamate +Oxaloacetate
2. Oxaloacetate+NADH+H^+⟶L-Malate+ NAD^+

The change in optical density at 340 (Hg 334, Hg 365) nm per unit time is a measure of the GOT activity.

(2) Glutamate-Pyruvate Transaminase (GPT):

L-Alanine: 2-oxoglutarate aminotransferase.

For assaying the activity of GPT, the method of Taylor *et al.* (1975) was used.

Principle:

1. 2-Oxoglutarate+L-Alanine $\xrightarrow{GPT}$ L-Glutamate +Pyruvate.
2. Pyruvate+NADH+H^+ $\xrightarrow{LDH}$ L-Lactate+NAD^+.

The change in optical density at 340 (Hg 334, Hg 365) nm per unit time is a measure of the GPT activity.

(3) Alkaline Phosphatase (ALP):

This is an optimised standard method conforming to the recommendations of the Deutsche Gesellschaft für Klinishe Chemie.

Principle:

P-nitrophenylphosphate+H_2O $\xrightarrow{ALP}$ phosphate-p-nitrophenol

N.B. All the three tests were done using Boehringer kits.

(4) *Statistical Analysis*

Student *t* test was used for analysis of the data.

RESULTS

Fig. (1. a) shows the levels of serum alkaline phosphatase of one month old animals. The drug was given for the first group of mothers in the first trimester,the second group in the second trimester and the third group in the third trimester,

However, in the first trimester there was no significant change ($p>0.05$) but the three different doses showed a transient decrease compared with the control one. For the second trimester 10 and 20 mg doses did not show much difference from the control but the 30 mg dose showed a transient decrease. For the third trimester 10 mg dose did not show a significant change. However, there was a transient decrease for the other two doses.

Fig. (1b) shows the levels of serum alkaline phosphatase of two months old animals. The mothers were treated in the same way as described above. For the first trimester ALP levels were close to control for the three different doses. However, in the second trimester only the 30mg dose showed a transient decrease in ALP levels. For the third trimester ALP decreased significantly ($p<0.05$) for the 10mg dose. The decrease in ALP for the other two doses were transient.

Fig. (2a) shows the levels of serum glutamate oxaloacetate transaminase (GOT) of one month old animals. The mothers were treated as described above. For the first trimester, there was highly significant rise ($p<0.01$) in GOT levels for 30 mg dose, whereas for other doses the levels were almost as normal. There was no significant change in the second trimester for the three different doses. For the third trimester, the three doses showed a transient rise in GOT levels.

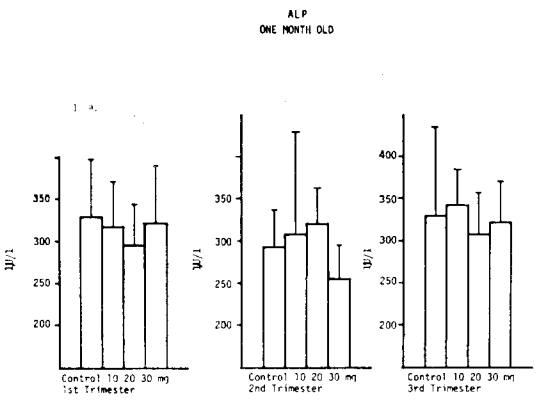

Fig. (**1a**): Serum alkaline phosphatase levels of one month old offspring. The drug was administered to different groups of animals during the different stages of pregnancies. Each value represents the mean of 10 animals ±SD.

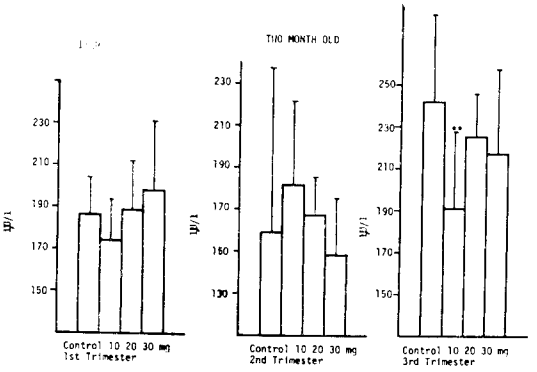

Fig. (**1b**): Serum Alkaline phospatase levels of two month old offspring. Each value represents the mean of 10 animals±SD
**significantly different from corresponding control ($p<0.05$)

Fig. (2b) shows the levels of GOT of two months old animals. There was a marked rise in GOT levels for 30mg dose but it was not significant ($p>0.05$) for the first trimester. The first trimester. The effect of the other two doses was negligible. GOT was significantly increased ($p<0.05$) for the 30mg dose and 10mg dose for the second and third trimester respectively. The change in the enzyme level was relatively

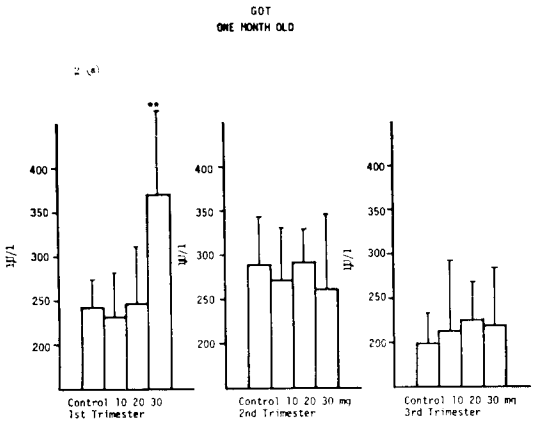

Fig. (**2a**): Serum glutamate oxaloacetate transaminase levels of one month old offspring. The drug was administered to different groups of animals during the different stages of pregnancies. Each value represents the mean of 10 animals±SD.
**Highly significant diffefference from corresponding control ($p<0.01$).

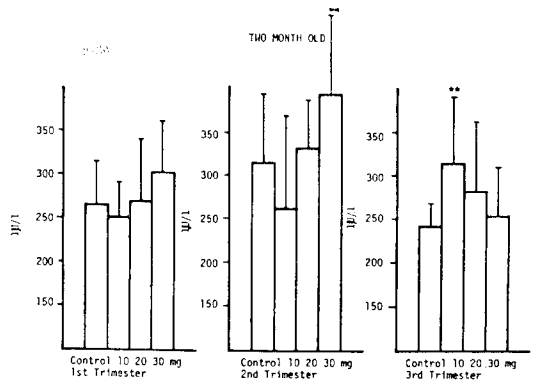

Fig. (**2b**): Serum glutamate oxaloacetate transaminase levels of two month old offspring. Each value represents the mean of 10 animals± SD.
**Significantly different from corresponding control ($p<0.05$)

small for the other two doses in the second trimester where the third trimester there was a slight increase for 20 and 30mg doses.

Fig. (3a) shows the levels of serum glutamate pyruvate transaminase (GPT) of one month old offspring. The mothers were treated as described

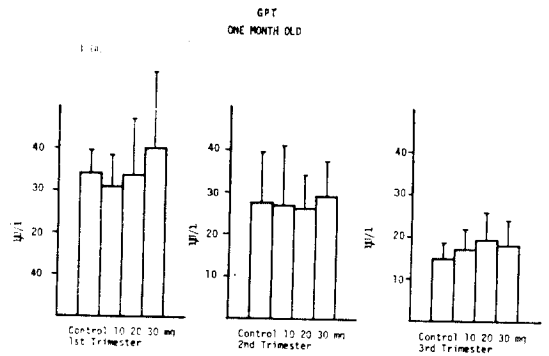

Fig. (3a): Serum glutamate pyruvate pyruvate transaminase levels of one month old offsp ring. The drug was administered to different groups of animals during the different stages of pregnancies. Each value represents the mean of 10 animals±SD.

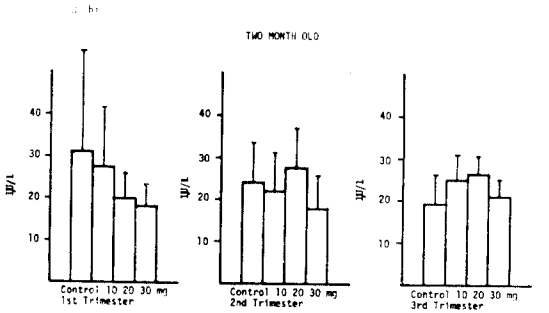

Fig. (3b): Serum glutamate pyruvate transaminase levels of two month old offspring. Each value represents the mean of 10 animals ±SD.

above.

Fig. (3b) shows the levels of GPT of two month old offspring. the level of GPT remained relatively close to control for the different doses given in the three trimesters for one and two month old offspring.

DISCUSSION

Pyrantel pamoate was found to be extremely well tolerated. This is not surprising as it is poorly absorbed from the gastrointestinal tract. This compound has an extremely wide margin of safety.

High dose chronic toxicity experiments in beagles have shown no serious toxic effects[4].

The decrease in plasma ALP activity of the suckling offspring to whose mothers was administered the drug has not been previously reported and may be of considerable importance. However the decrease in ALP activity by the prenatal pyrantel was not significant in the three trimesters (Fig. 1a, 1b) experiment, but nevertheless there was a transient decrease in most cases. As young animals have a high plasma ALP related to growth rate and osteoblastic activity[7], the effect of the pyrantel pamoate may well be a depression of this activity leading to decreased ALP production. Administration of this drug during pregnancy could possibly lead to impaired bone growth in the offsprings.

The decrease in ALP activity was obvious in one month old animals where the drug was given in first and second trimester. This change was not noticed clearly in two month old animals for the same experiments. On the other hand when the drug was given in the third trimester, the activity of ALP was reduced in one and two month old mice. These observations may indicate that the drug could be more toxic on the fetus in late pregnancy, where in early pregnancy the toxicity was mild and bone growth was restored to normal as the animal grew up.

It has been reporled by Snow[4] that treatment of young dogs with pyrantel pamoate at the recommended dose (5mg/kg) causes significant decrease in ALP activity, when the drug was given to young dogs every second day for two weeks, there was an initial decline in ALP activity, then a fairly constant level was established.

The new level ef activity on repeated administration of pyrantel pamoate may have occurred because complete osteoblastic ALP inhibition resulted after the first and second doses. The same author also reported that at maturity ALP activity remains fairly constant. Although there is species difference these results are in agreement with our findings.

The above data are preliminary. Further experiments will be carried out. Isoenzymes of alkaline phosphatase as well as gamma-glutamyl transferase will be measured. The findings will then confirm the origin of alkaline phosphatase.

Although GPT levels were not changed significantly there was a significantly there was a significant increase in GOT levels in some cases, when the drug was given in large doses (Fig. 2a. 2b). The increase in GOT levels was not constant.

The blood picture of the same animals showed no significant change in the haematocrit nor in the red cell count (unpublished data). The reticulocyte count was normal. These findings show that there is no destruction of red cells, which imply that the origin of GOT might not be the red cells. An explanation of these results is somewhat difficult.

Pitts and Migliardi[3] showed that the incidence of abnormalities in laboratory parameters in patients treated with pyrantel pamoate was greater in case of GOT levels in two different trials. In fact the number of patients who showed increased GOT levels were the highest. Although there is species difference, but the results follow the same pattern. However, there is no such study performed on mice before, in general one can assume that the drug may have a toxic effect on liver cells or cardiac muscles.

As these results are preliminary, further experiments to investigate the problem will be carried out. Lactate dehydrogenase and creatinine phosphokinase (MB isoenzyme) will be measured.

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