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Prenatal Effect of Pyrantel Pamoate on Several Hematological Parameter of Offsprings in Mice

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Abstract□In attempt to develop a drug delivery system using serum albumin microspheres, bovine serum albumin microspheres containing antitumar agent, cytarabine, were prepared. The shape, surface characteristics, size distribution, behavior of in vivo distribution, drug release behavior, and degradation of albumin microspheres in animal liver tissue homogenate and proteolytic enzyme were investigated.

The shape of albumin microspheres was spherical and the surface was smooth and compact. The size distribution of the albumin microspheres was effected by dispertion forces during emulsification and albumin concentration. Distribution of albumin microspheres after imtravenous administration in rabbit was achieved immediately. *In vitro*, albumin microsphere matrix was so hard that it retained most of cytarabine except initial burst during the first 10 minutes, and the level of drug release during the initial burst was affected by heating temperature, drug/albumin concentration ratio and size distribution. After drug release test, the morphology of albumin microspheres was not changed. Albumin microsphere matrix was degraded by the animal liver tissue homogenate and proteolytic enzyme. The degree of degradation was affected by heating temperature.

Keywords□Bovine serum albumin, drug delivery system, cytarabine, cottonseed oil, size distribution, surface characteristics of albumin micropheres, preparation of albumin microspheres, drug release from albumin microspheres, distribution of albumin microspheres after intravenous administration in rabbit.

Pyrantel pamoate (Combantrin(R), Antiminth[4]) as an anthelmintic drug has been indicated for use in *Enterobiasis vermicularis* (pin worms), *Ascaris lumbricoides* (round worms) and *Nactar americans* (hook worms)[1] infestations.

The anthelmintic activity is due to pyrantels 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 sale pyrantel pamoate which is partially absorbed[2].

Pyrantel pamoate is generally well tolerated. It has mild transient reaction related to gastrointestinal distress[3]. Transient rises in serum glutamate oxaloacetate transaminase have been seen in the treated patients[3].

The study performed by Snow[4] on greyhounds showed no significant changes in serum glutamate pyruvate transaminase 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. He also reported that red blood cell count remained unchanged. Pyrantel pamoate has not been found to be teratogenic in rabbits and rats[5], but recently it has been reported that it has teratogenic effects in mice[8]. However, it has not been studied fully in humans, and more studies in this respect are needed.

An investigation into the possibility of pyrantel pamoate having toxic haematological effects on pregnant mice progenies was carried out by doing complete blood cell count (CBC) as well as the differential count.

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MATERIALS AND METHODS

Animals Used:

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 (27x21x14 cm), on sawdust beeding, 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 throughout at 24 + 4°C.

Determination of the 1st day of pregnancy:

Each female is mixed with one male in one cage for mating. Each female was observed next day in the early morning for a vaginal plug. The 1st time the vaginal plug was observed, was considered the 1st day of pregnancy. Each mated female was separated individually in a private cage under food and water ad libitum.

Stages of pregnancy:

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

Drugs used and dosages selection:

Pyrantel pamoate (Combantrin(R)) 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 a base. The oral LD_{50} for the drug in mice is 200 mg/kg[7]. Pilot experiments were carried out to select the suitable sublethal oral dose which should be used without appearance of gross toxic effects on the mother and their offspring[8].

It had been noticed that a dose of 30 mg/Kg of oral pyrantel pamoate suspension as a base which has no gross toxic symptoms on the pregnant mice and their offspring, was considered as the suitable large dose. Therefore, three oral doses of the drug as a base were selected and used daily for each group of mice during each stage of pregnancy. Those used doses are; small (10 mg/kg), intermediate (20 mg/kg) or large (30 mg/kg).

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 eachstage was given normal saline 10 ml/kg.

Administration of the drugs:

At the beginning of the 1st, 2nd or 3rd stage of pregnancy, four groups, 10 of each, of pregnant mice were used. The 1st, 2nd or 3rd group were given orally 10 mg, 20 mg or 30 mg/kg/day body weight of the drug respectively for seven consecutive days. The 4th control group was administered orally, 10 ml/kg/day body weight saline solution for seven consecutive days too. Each group of pregnant animals received at least 6 doses.

Blood collection and CBC studies:

For each stage of pregnancy and for each dose of drug, subgroups of 10 offspring each were selected by random for blood collection and CBC studies. The blood was collected from one and two month old offspring into EDTA containing tubes. Coulter counter model (S Plus II) was used for CBC while differential counts were performed manually by the same technician throughout. Student T test was used for statistical analysis of the data.

Table I. Effect of pyrentel pamoate on CBC of mice progenies. The drug was given daily during the first stage of pregnancy. Each value represents the means of 10 animals ± SD.

Treatments	WBC × $10^9/l$	RBC × $10^{12}/l$	Hgb g/dl	HCT ratio	PLT × $10^9/l$
		One month old			
Control (A)	6.1 ±2.59	6.38±0.54	11.78±0.10	0.34±0.03	662.6 ±176.27
10 mg (B)	6.68±2.04	6.7 ±0.39	12.39±0.67	0.35±0.01	738.60±167.26
20 mg (C)	5.10±1.56	6.27±0.59	11.74±1.08	0.35±0.04	622.60±300.82
30 mg (D)	5.42±0.57	6.87±0.38	12.44±0.5	0.36±0.03	601.90±185.18
		Two-month old			
Control (A)	6.03±0.93	8.58±0.43	14.71±1.19	0.42±0.03	565.56±205.07
10 mg (B)	5.16±1.13	8.30±0.66	15.01±1.07	0.42±0.04	629.40±186.00
20 mg (C)	5.93±1.36	7.48±1.90	14.88±0.62	0.88±0.10	440.20±143.64
30 mg (D)	5.42±1.27	8.1 ±0.65	14.44±2.02	0.44±0.03	495.11±246.25

RESULTS

The prenatal effect of pyrantel pamoate on CBC leukocyte differential count of one- and two-month old offspring where the drug was given during the first stage of pregnancy is shown in tables I, II. In one and two month old drug-treated offspring, leukocytes counts, RBC, Hgb, HCT and PLT showed no significant changes from the control. The drug also showed no significant changes in leukocytes differential counts in these animals.

Tables III, IV show the prenatal effect of pyrantel pamoate on CBC and leukocyte differential counts of one and two month old offspring, where the drug was given during the second stage of pregnancy. The drug showed no significant changes in the parameters.

Tables V, VI show the prenatal effect of pyrantel pamoate on CBC and differential counts of one and two month old offspring, where the drug was given during the third stage of pregnancy. WBC and leukocyte differential counts in one and two month old offspring showed no significant changes from the control values. The changes in RBC, Hgb, HCT and PLT were also not

Table II. Effect of pyrantel pamoate on leukocyte differential counts of mice. The drug was given daily during the first stage of pregnancy. Each value represents the mean of 10 animals ± SD.

Treatments	% Polymorphocytes	% Lymphocytes →	% Monocytes	% Eosinophils
		One month old		
Control (A)	14.88±3.80	83.00±4.72	1.38±1.30	2.75±1.5
10 mg (B)	16.10±7.48	79.80±8.88	2.30±1.49	2.57±1.81
20 mg (C)	13.88±6.40	83.00±5.04	1.57±2.63	1.63±1.92
30 mg (D)	13.10±2.73	82.00±3.20	2.70±1.70	2.20±1.55
	12	Two month old	0 89	
Control (A)	16.44±6.83	81.33±6.06	1.50±0.16	2.71±1.11
10 mg (B)	12.70±3.77	84.20±4.10	2.11±1.00	1.80±1.10
20 mg (C)	13.40±6.35	83.00±6.41	2.37±1.51	1.71±0.95
30 mg (D)	13.67±2.	83.11±2.20	1.37±0.↓	2.00±1.32

Table IV. Effect of pyrantel pamoate on leukocyte differential count of mice pregenies. The drug given daily to the mothers during second stage of pregnancy. Each value represents the mean of 10 animals ± SD.

Treatments	% Polymorphocytes	% Lymphocytes	% Monocytes	% Eosinophils
		One month old		
Control (A)	19.5±5.5	78.3 ±6.5	1.5 ±1.1	0.7 ±0.95
10 mg (B)	18.9±6.5	78.8 ±6.97	1.7 ±0.7	0.6 ±0.97
20 mg (C)	16.6±5.4	81.3 ±6.1	1.00±0.9	0.67±0.87
30 mg (D)	16.9±6.30	81.2 ±7.2	1.4 ±0.7	0.5 ±1.27
		Two month old		
Control (A)	15.4±6.2	79.5 ±4.6	2.00±1.3	1.9 ±2.2
10 mg (B)	12.8±2.5	83.4 ±3.3	2.2 ±1.1	1.5 ±1.6
20 mg (C)	14.4±4.5	82.9 ±3.9	1.5 ±0.7	1.3 ±1.5
30 mg (D)	18.3±7.3	79.00±8.8	1.8 ±1.4	0.9 ±1.4

Table III. Effect of pyrantel pamoate on complete blood count of mice progenies. The drug was given daily to the mothers during the second stage of pregnancy. Each value represents the mean of 10 animals ± SD

Treatments	WB×10^9/*l*	RBC×10^{12}/*l*	Hgb g/d*l*	HCT ratio	PLT×10^9/*l*
			One month old		
Control (A)	4.8 ±0.9	6.6 ±0.5	12.04±0.95	0.36±0.3	570.5±203.3
10 mg (B)	4.9 ±1.00	6.2 ±0.6	11.6 ±0.9	0.35±0.04	669.5±118.2
20 mg (C)	5.7 ±1.6	6.5 ±1.2	11.8 ±1.9	0.34±0.06	694.3±236.5
30 mg (D)	5.4 ±1.8	6.7 ±0.4	11.9 ±0.73	0.37±0.02	736.4±171.3
			Two month old		
Control (A)	4.35±0.65	8.20±1.2	15.3 ±0.7	0.4 ±0.06	641.3±238.3
10 mg (B)	4.75±1.5	7.8 ±1.4	15.1 ±0.7	0.45±0.05	463.7±221.1
20 mg (C)	5.2 ±1.75	7.9 ±1.3	14.9 ±0.9	0.41±0.06	675.6±330.4
30 mg (D)	4.5 ±0.9	8.4 ±0.7	15.3 ±1.2	0.4 ±0.04	736.0±485.4

Table V. Effect of pyrantel pamoate on complete blood count of mice progenies. The drug was given daily to the mothers during the third stage of pregenancy. Each value represents the mean of 10 animals ± SD

Treatments	WBC × $10^9/l$	RBC × $10^{12}/l$	Hgb g/dl	HCT ratio	PLT × $10^9/l$
			One month old		
Control (A)	4.73 ± 1.12	6.58 ± 0.73	11.84 ± 1.57	0.35 ± 0.1	543.3 ± 181.3
10 mg (B)	5.23 ± 1.22	6.97 ± 0.47	12.64 ± 0.77	0.38 ± 0.03	620.4 ± 194.94
20 mg (C)	5.46 ± 1.53	7.1 ± 0.64	12.91 ± 1.01	0.4 ± 0.06	642.3 ± 140.2
30 mg (D)	5.45 ± 1.91	7.15 ± 0.4	12.81 ± 0.61	0.38 ± 0.03	606.1 ± 145.79
			Two month old		
Control (A)	5.45 ± 1.83	8.25 ± 0.53	15.24 ± 1.02	0.45 ± 0.05	989.4 ± 303.97
10 mg (B)	5.2 ± 1.27	8.79 ± 0.43	15.17 ± 0.7	0.45 ± 0.03	826.9 ± 167.5
20 mg (C)	4.7 ± 1.44	8.5 ± 0.47	14.88 ± 0.59	0.45 ± 0.04	853.9 ± 219.1
30 mg (D)	5.48 ± 1.54	8.18 ± 0.81	15.6 ± 0.3	0.44 ± 0.05	809.7 ± 271.6

statistically significant in these animals.

DISCUSSION

It is obvious from the results shown that the different doses of the drugs used in the trial had no effect of significance on the hematologic parameters measured. Pitts and Migliardi[3] studied the side effects of the drug in the total of 1506 patients. They showed that the drugs had no significant effect on hematological picture.

Our own showed a decrease in plasma alkaline phosphatase activity and a rise in plasma aspartate amino transferase activity in the same animals for some doses of the drugs[9].

This may lead to assumption that the drug may have a toxic effect on liver cells. Although there is no significant hematological effect, it is not recommended for use in pregnant women unless deemed essential for the welfare of the patient.

Table VI. Effect of pyrantel pamoate on leukocyte differential count (LDC) of mice progenies. The drug was given daily during the third stage of pregnancy. Each value represent the mean of 10 animals ± SD.

Treatments	% Polymorphocytes	% Lymphocytes	% Monocytes	% Eosinophils
		One month old		
Control (A)	14.00 ± 4.75	82.3 ± 5.06	2.75 ± 3.37	1.29 ± 2.33
10 mg (B)	20.3 ± 14.18	78.1 ± 13.85	1.00 ± 0.94	0.86 ± 0.9
20 mg (C)	14.3 ± 2.16	84.2 ± 2.25	0.9 ± 0.74	0.6 ± 0.52
30 mg (D)	21.00 ± 9.62	75.8 ± 10.45	1.7 ± 0.48	1.7 ± 1.95
		Two month old		
Control (A)	13.1 ± 7.49	84.6 ± 7.80	1.3 ± 0.68	1.00 ± 0.94
10 mg (B)	12.3 ± 4.00	84.2 ± 3.08	1.5 ± 1.1	1.6 ± 1.1
20 mg (C)	16.9 ± 5.3	80.4 ± 5.4	1.11 ± 0.33	1.89 ± 1.89
30 mg (D)	12.56 ± 4.70	84.4 ± 5.8	1.67 ± 1.5	1.33 ± 1.4

SUMMARY

The possible toxic effect of pyrantel pamoate as anthelmintic drug on pregnant mice was investigated. The drug was given in different doses to pregnant mice during the first, second and third, stages of pregnancy. Complete blood cell count as well as differential count were measured in one- and two-month old offspring. The drug has no effect of significance on those hematological parameters.

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