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Effects of Quinine and Fansidar and Their Combination on Bovans-Type Chicks

[1]Warda S. Abdel Gadir, [2]Mohy Edeen, [2]D. Abu Alazaim,
[3]Amel O. Bakhiet and [3]I.M.T. Fadlalla
[1]Food Research Center, Ministry of Science and Technology
P.O. Box 213, Khartoum North, Sudan
[2]Faculty of Science and Technology, El Neelain University, P.O. Box 12702, Khartoum
[3]Collage of Veterinary Medicine and Animal Production, Sudan University of
Science and Technology, P.O. Box 204, Khartoum North, Sudan

Abstract: This study was done on 40 Bovans-type chicks to investigate the possible toxic effects of the therapeutic doses of the antimalarial drugs, Quinine and Fansidar and their combined doses. After two weeks (adaptation period), the drugs were dissolved in distilled water in concentrations of 4.33 mg mL day^{-1} for Quinine, 4.19 mg mL day^{-1} for Fansidar and their mixture (4.33 mg Quinine plus 4.19 mg Fansidar) mL day^{-1} and given orally to Bovans chicks for two weeks. The effects on growth and tissues were investigated. After one week, there was no change in growth and at post-mortem examination, there was congestion of liver in all tested chicks and haemorrhage on the heart of chicks that had been given Fansidar. Serobiochemical changes were increase in the activities of AST, ALT and in concentration of albumin, uric acid, total protein and globulin and decrease in cholesterol levels. There were decreases in haemoglobin, PCV, MCV and MCH values. At the end of two weeks, there was depression in growth of tested chicks, degeneration of the liver of chicks that had been given Quinine and mixture of Quinine plus Fansidar and cardiac haemorrhage in chicks that had been given fansidar and or quinine plus fansidar with increases in AST, ALT activities and in total protein concentration with decreases in globulin levels and PCV values.

Key words: Quinine, fansidar, chicks

Introduction

Quinine and the combination of Pyrimethamine and sulfadoxine (Fansidar) is the most important antiprotozoan drugs used to treat acute attacks of malaria caused by susceptible strains of *Plasmodium falciparum* in case of chloroquine-resistant *P. falciparum* (Laurence *et al*., 1997).

Quinine is derived from the bark of the Cinchona tree, a traditional remedy for intermittent fever from South America. The alkaloid quinine was purified from the bark in 1820 and it has been used for the treatment and prevention of malaria since that time (Philip and Robert, 2001). It selectively inhibits the plasmodial nucleic acid synthesis by interfering with the template function of DNA; this is accomplished by a preferential hydrogen bonding with purine molecules and a subsequent intercalation of the Quinine molecule between stacked base pair in the DNA helix. In this way, Quinine prevents transcription and translation, reducing DNA and RNA synthesis (Joseph, 1990).

Acute toxicity of Quinine was reported in adults, 75% of patients were symptomatic and 17% had visual or adverse cardiovascular effects (Dyson *et al*., 1985). The patients may present with

Corresponding Author: Amel O. Bakhiet, Collage of Veterinary Medicine and Animal Production,
Sudan University of Science and Technology, P.O. Box 204, Khartoum North, Sudan
Tel: +249912347090 Fax 249183497001

stupor, coma, confusion, delirium or have extensive muscle weakness with or without convulsions (Wolf *et al*., 1992). Intravenous administration may produce venous thrombosis whereas intramuscular and subcutaneous injection can result in tissue necrosis. The clinical toxicity is the same as in oral administration and the onset is more rapid (Bateman *et al*., 1985). Chronic toxicity includes Central Nervous System (CNS), cardiovascular, gastrointestinal (GI), dermatologic, haematologic and renal toxicity. Cinchonism may occur with therapeutic doses (Reynolds, 1996). Progressive visual loss following ingestion of excessive amounts of Indian tonic water has been reported (Horgan and Williams, 1995). The major causes of morbidity in Quinine overdose include reversible renal failure, cinchonism, prolonged hearing deficits and blindness; the skin is often hot and flushed initially then may become cold and pale (Rollo, 1975; Dannenberg *et al*., 1983; Licciardello and Stanbury, 1984; Marr, 1985; McEvoy, 1994). Death generally follows cardiac disturbances, renal failure, acute haemolytic anemia and respiratory arrest (Dannenberg *et al*., 1983; Licciardello and Stanbury, 1984).

Fansidar is a fixed combination of the sulfonamide sulfadoxine (500 mg per tablet) and pyrimethamine (25 mg per tablet); it is a folate antagonist combination class of drugs (Philip and Robert, 2001). Pyrimethamine acts synergistically with sulfadoxine to prevent the plasmodial DNA synthesis by inhibiting their folic acid metabolism (Laurence *et al*., 1997).

The toxicity of this drug resides in their dihydropteroate synthase and dihydrofolate reductase inhibiting ability. The high doses and use for prolonged periods can cause the symptoms of folic acid deficiency. These include bone marrow depression and megaloblastosis and it is readily reversible by the administration of folic acid or by cessation of treatment (Joseph, 1990). In endemic areas, where continual use is expected, the simultaneous administration of folic acid is recommended. Because of its membrane-penetrating ability, the use of this drug in pregnant woman is not advisable (Joseph, 1990).

The study was planned in order to examine whether 14 days oral administration of the therapeutic doses of Quinine and Fansidar and the combination of these therapeutic daily doses would be toxic to Bovans chicks or otherwise.

Materials and Methods

Chicks and Drugs Administration

Forty, one-day-old Bovans cockerels were obtained from Coral Company Ltd., Khartoum and reared in pens within the premises of the College of Veterinary Medicine and Animal Production, Sudan University of Science and Technology, Khartoum North, under illumination at night and early morning with feed and drinking water provided *ad libitum*. At the age of fourteen days, the chicks were divided at random into four groups, each of 10. Chicks in group 1 were the controls and fed starter ration (Table 1). Quinine and Fansidar drugs were bought from a pharmacy at Khartoum Central Market and given in oral doses to chicks for 14 days at 4.33 mg day of Quinine (group 2), 4.19 mg/day of Fansidar (group 3) and 1:1 mixture of both drugs (group 4). The daily doses of the drugs were dissolved in 1 mL of distilled water for each chick in the test groups. Five chicks from each group were slaughtered after one week and the remaining chicks were slaughtered at the end of week 2 for pathological examination.

Table 1: Composition of the diet for chicks

Ingredients	Percentage
Sorghum	62
Sesame cake	14
Groundnut cake	12
Wheat bran	5
Marble dust	1
Dicalcium phosphate	1
Super concentrate	5
Total	100

Clinical signs and body weight and weight gains were recorded. Necropsies were carried out to identify gross lesions and the specimens of the liver, kidney and heart were collected immediately after slaughter of birds and fixed in 10% neutral buffered formalin, embedded in paraffin wax, sectioned at 5 μm and stained routinely with haematoxylin and eosin (H and E) using Harris's haemalum.

Laboratory Assays

Blood samples were obtained from the cervical blood vessels of chicks during slaughter into clean bottles for serum analysis and haematology. Sera were analyzed for the activities of aspartate aminotransferase (AST), alanine aminotransferase (ALT) and for the concentrations of total protein, albumin, globulin, cholesterol and uric acid by using commercial kit (Linear Chemicals, Barcelona, Spain). Blood samples were examined for Haemoglobin Concentration (Hb), Packed Cell Volume (PCV), Red Blood Cell (RBC) counts, Mean Corpuscular Volume (MCV), Mean Corpuscular Haemoglobin (MCH) and Mean Corpuscular Haemoglobin Concentration (MCHC). These methods were described by Schalm *et al*. (1975).

Statistical Analysis

The significance of differences between means was compared at each time point using Duncan's multiple range test after ANOVA for one-way classified data (Snedecor and Cochran, 1989).

Results

Clinical Signs

The dosing schedule and survival time of the chicks orally given Quinine, Fansidar or their mixture are summarized in Table 2. Generally, there was no death among the chicks during the experimental period. The control chicks in group 1 remained clinically healthy during the experiment and were humanely slaughtered on day 14. Chicks in groups 2-4 showed dullness, inappetence and diarrhea (from day 2 to day 9). These clinical signs appeared immediately after giving the respective doses and disappeared during 1 to 2 h except the diarrhea which did not disappear till the end of the experiment. Signs were severe in groups 2 and 3.

Effects on Growth

The effects of the two drugs given alone or combined on chick's growth are summarized in Table 3. At week 2, there was a significant decrease ($p<0.05$) in body weights and weight gains of test chicks in groups 2, 3 and 4 than the control chicks (group 1).

Table 2: The dosing schedule and survival time of chicks treated with the Quinine, Fansidar or their mixture for two weeks

Groups	No. of chicks at day 0	Oral dose of drug (mg day)	No. of chicks slaughtered at week 1	No. of chicks slaughtered at week 2
Group 1 (Control)	10	Nil	0	5
Group 2	10	4.33 Quinine	5	5
Group 3	10	4.19 Fansidar	5	5
Group 4	10	4.33 Quinine+4.19 Fansidar	5	5

Table 3: Growth changes of chicks orally given Quinine, Fansidar or their mixture for two weeks

Groups	Body weights at day 0 (g)	Weight gains at week 1 (g)	Weight gains at week 2 (g)	Onset of clinical signs (day)	Mortality
Group 1 (Control)	63±1.67	31±1.21	48±2.08	Nil	0
Group 2 (Quinine 4.33 mg)	65±1.43^{NS}	39±1.65^{NS}	26±1.95*	2	0
Group 3 (Fansidar 4.19 mg)	67±2.05^{NS}	33±1.32^{NS}	28±0.87*	2	0
Group 4 (mixture of both drugs)	64±1.86^{NS}	41±1.73^{NS}	30±1.81*	2	0

Values are mean±SE, * = significantly different at $p<0.05$, NS = Not Significant

Pathological Changes

After one week, chicks in groups 2, 3 and 4 showed severe hepatic congestion. Chicks in group 3 showed severe haemorrhage on the heart. There were no changes in the control chicks (group 1). No gross lesions were seen in the gizzard, proventriculus, intestine, kidneys or spleen of the test chicks. At the end of two weeks, the liver of chicks in groups 2 and 4 was degenerated with severe cardiac haemorrhage in groups 3 and 4. Although 4.33 mg day of Quinine (group 2) and Fansidar at 4.19 mg day (group 3) singly, produced focal hepatocellular necrosis, the combined doses of both drugs caused more severe necrosis (Fig. 1).

Laboratory Results

The biochemical changes are summarized in Table 4. There were significant increases in AST activity ($p<0.05$) in groups 2-4 at weeks 1 and 2. Serum ALT activity also showed a significant increase ($p<0.05$) in group 2 at weeks 1 and 2 and in group 3 at week 1. Globulin concentration was increased significantly ($p<0.05$) in group 3 at week 1. Albumin concentration in group 2 showed significant increases ($p<0.05$) at week 1. Also there was significant increase in the concentration of total protein in group 3 at week 1, while globulin concentration showed significant increase in group 4 at week 2. Total protein and globulin concentration in group 2 and globulin concentration in group 3 showed significant decrease ($P<0.05$) at week 2. Cholesterol concentration was significantly lower ($p<0.05$) in all tested groups than the control (group 1) at week 1. There were significant increase ($p<0.05$) in uric acid level in group 3 at week 1.

Haematological changes are presented in Table 5. There was a significant decrease ($p<0.05$) in haemoglobin concentration (Hb) in group 3 at week 1 and in group 4 at week 2, Packed Cell Volume (PCV) percentage was decreased in group 3 at week 1 and in groups 3 and 4 at week 2. Mean Corpuscular Volume (MCV) and Mean Corpuscular Haemoglobin (MCH) values were significantly decreased ($p<0.05$) in groups 2 and 3 at week 1 when compared with the control chicks in group 1. There were no significant changes in the values of RBC, MCV, MCH and MCHC in the test groups after 2 weeks.

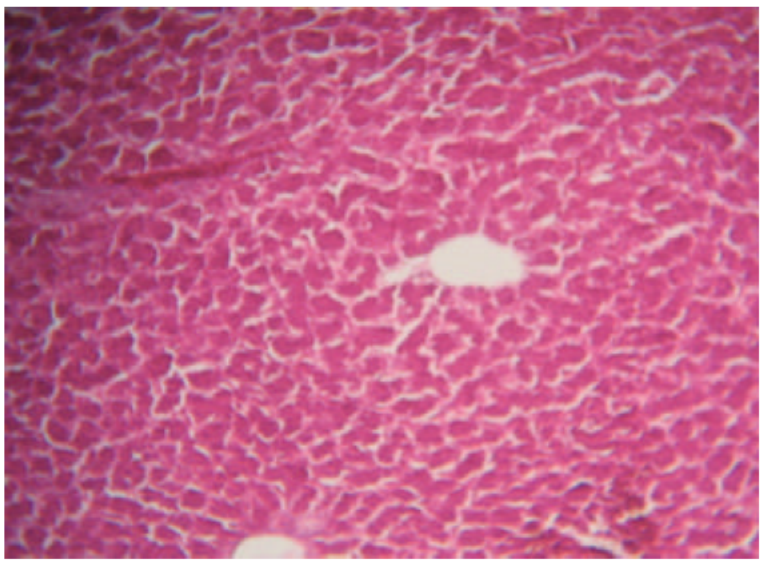

Fig. 1: Severe focal hepatocellular necrosis in chick given combined doses of Quinine (4.33 mg day) and Fansidar (4.19 mg day) for one week. H and EX90

Table 4: Serobiochemical changes of chicks given Quinine, Fansidar or their mixture for two weeks

Parameters	Group 1 (Control)	Group 2 (Quinine 4.33 mg)	Group 3 (Fansidar 4.19 mg)	Group 4 (Mixture of both drugs)
Week 1				
AST (U L^{-1})	18.20±0.60	64.80±0.97*	40.80±1.40*	31.50±1.30*
ALT (U L^{-1})	15.60±0.93	32.60±1.86*	31.20±2.06*	15.00±1.08^{NS}
Cholesterol (mg dL^{-1})	156.50±5.7	98.70±8.4*	105.10±1.2*	128.40±6.8*
Uric acid (mg dL^{-1})	4.64±0.19	5.25±0.67^{NS}	5.70±0.11*	5.05± 0.38^{NS}
Total protein (g dL^{-1})	2.54±0.13	2.82±0.28^{NS}	3.36±0.16*	2.53±0.40^{NS}
Albumin (g dL^{-1})	1.50±0.08	1.74±0.31*	1.52±0.13^{NS}	1.39±0.15^{NS}
Globulin (g dL^{-1})	1.04±0.20	1.08±0.33^{NS}	1.83±0.41*	1.14±0.27^{NS}
Week 2				
AST (U L^{-1})	18.20±0.60	27.40±2.94*	23.60±0.75*	26.00±1.25*
ALT (U L^{-1})	15.60±0.93	34.00±5.32*	15.40±0.68^{NS}	18.50±2.63^{NS}
Cholesterol (mg dL^{-1})	156.50±5.7	146.70±11.3^{NS}	153.10±3.6^{NS}	138.40±4.7^{NS}
Uric acid (mg dL^{-1})	4.64±0.19	4.47±0.29^{NS}	4.38±0.36^{NS}	4.44±0.11^{NS}
Total protein (g dL^{-1})	2.54±0.13	1.82±0.08*	2.45±0.4^{NS}	2.67±0.19^{NS}
Albumin (g dL^{-1})	1.50±0.08	1.25±0.02^{NS}	1.41±0.07^{NS}	1.29±0.09^{NS}
Globulin (mg dL^{-1})	1.04±0.20	0.57±0.12*	0.62±0.17*	1.38±0.37

*Values are mean±SE, * = Significant different at $p<0.05$, NS = Not significant

Table 5: Haematological changes of chicks orally given Quinine, Fansidar or their mixture for two weeks

Parameters	Group 1 (Control)	Group 2 (Quinine 4.33 mg)	Group 3 (Fansidar 4.19 mg)	Group 4 (Mixture of both drugs)
Week 1				
Hb (g dL^{-1})	6.70±0.35	6.70±0.27^{NS}	4.90±0.17*	5.90±0.25^{NS}
PCV (%)	19.20±1.28	18.80±0.37^{NS}	13.80±0.58*	16.90±0.40^{NS}
RBC (10^6 mm^3)	2.56±0.09	3.14±0.51^{NS}	2.75±0.46^{NS}	2.56±0.26^{NS}
MCV (m^3)	75.00±7.7	59.90±4.1*	50.20±3.2*	66.00±7.1^{NS}
MCH (pg)	26.20±1.80	21.30±1.30*	17.80±1.15*	23.10±2.59*
MCHC (%)	33.90±0.28	35.10±1.18^{NS}	35.40±0.62^{NS}	34.90±0.59^{NS}
Week 2				
Hb (g dL^{-1})	6.70±0.35	6.20±0.33^{NS}	6.00±0.26^{NS}	5.90±0.32*
PCV (%)	19.20±1.30	17.40±0.24^{NS}	16.60±0.93*	16.60±1.29*
RBC (10^6 mm^3)	2.56±0.09	2.53±0.41^{NS}	2.41±0.50^{NS}	2.30±0.29^{NS}
MCV (m^3)	75.00±6.7	68.80±8.5^{NS}	68.90±7.7^{NS}	72.20±8.6^{NS}
MCH (pg)	26.20±1.80	24.50±4.10^{NS}	24.90±1.89^{NS}	25.70±1.55^{NS}
MCHC (%)	33.30±1.10	35.50±1.67^{NS}	35.90±1.28^{NS}	35.70±1.49^{NS}

Values are mean±SE, * = Significantly different at $p<0.05$, NS = Not significant

Discussion

In one-day-old Bovans-type chicks, the 14 days pretrial period with the identical well balanced ration was to achieve weight uniformity by the start of the experiment. The period was also to acclimate chicks to the poultry house environment at the College of Veterinary Medicine and Animal Production at Kuku, Khartoum North and to allow unhealthy ones to be eliminated.

The present study showed that both Quinine and Fansidar drugs were not lethal to Bovans chicks when given orally at 4.33 and, 4.19 mg day respectively or their combination for two weeks.

The present study has shown that the daily oral doses of Quinine and Fansidar are toxic to chicks and their toxicity is characterized by the development of anorexia, dullness, abdominal pain and diarrhea. These manifestations were attributed to cinchonism by Bateman and Dyson (1986).

The losses of appetite and growth weight depression at week 2 were probably associated with bitterness of both drugs (Simons *et al*., 2002).

The widespread congestion of the liver and haemorrhage on the heart might have been due to the alteration in the permeability of the capillaries after administration of the drugs (Glynne *et al*., 1999).

The decreased serum total protein, albumin and globulin concentrations in chicks given Quinine might be due to liver function impairment arising from hepatocytes injury (Chazquileres and Robert, 1996). The decrease in cholesterol concentration might be due to the decrease in lipoprotein synthesis. Serum uric acid concentration was increased due to kidney damage.

In the present study, injury to the liver probably contributed to the raised serum AST and ALT activities.

The relatively decrease in RBC counts and decrease in Hb, PCV, MCH and MCV values might be due to anemia (Kimber *et al*., 1965; Farver and Lavin, 1999) the anemia is microcytic normochromic at week one as indicated by low MCV and normal MCHC values or normocytic normochromic at week two as indicated by normal MCV and normal MCHC values.

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