EFFICACY AND SAFETY OF IVERMECTIN ADMINISTERED ORALLY TO INFECTED RABBITS WITH MANGE

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ABSTRACT

The purpose of this study was to evaluate the efficacy of oral formulation containing ivermectin for treatment of sarcoptic mange in rabbits . Twenty mixed-breed rabbits with a mean age of 9 months from a rabbit husbandry were enrolled in the study. Rabbits were treated with ivermectin at 400 µg /kg. body weight, one oral dose . No other treatment or environmental decontamination was performed during the trial .On Days 0, 7,14 and 28 after dosing all rabbits were examined, and epidermal debris was collected for microscopic examination. Clinical signs had subsided by Day 7 in 4/5 rabbits and almost no signs of recurrence were apparent in the following weeks. All epidermal samples were negative by Day 28. No adverse reactions were observed. Our investigations on serum biochemical parameters showed a significant differences than normal ranges, after 4 weeks post administration of the drug .Under the conditions of our study, oral formulation of ivermectin was a practical and well-tolerated means of treatment for mange in rabbits.

الملخص العربى

تأثير ودرجــة الأمــان لعقــار الأيفرمكتين المعطى عن طريق الفــم على الأرانب المصابــة بالجــرب

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أجرى هذا البحث لدراسة تأثير ودرجة الأمان لعقار الإيفرمكتين بإعطائه عن طريق الفم لعــلاج الجــرب فى الأرانب، أعطى العقار بجرعة 400 ميكروجرام لكل كيلو جرام وزن حى كجرعة واحدة.

وكانت النتائج إيجابية حيث إختفت الأعراض بعد 7 أيام من إعطاء العقار ولم يتم ملاحظة أى رد فعل سلبى نتيجة إستخدامه، وقد

لوحظت زيادات معنوية فى معدل كل من الترانس أمينيزسس والفوسفاتيز القاعدى والكرياتينين واليوريا فى مصل الدم عند 4 أسابيع بعد إعطاء العلاج، وكانت هذه الفروق المعنوية قريبة إلى المعدلات الطبيعية.

INTRODUCTION

Ivermectin is a broad spectrum antiparasitic widely used in control of internal and external parasites. B**arragny, (1987); Pandey, (1989); Ghoniem et al., (1992); Cutler, (1998); Sparsa et al., (2006)**.

Ivermectin, 22, 23- dihydroavermectin B1 is commercially important in human, veterinary medicine, and pesticides. It is currently synthesized by chemical reduction of the double bond between C22 and C23 of avermectin B1a (>80%) and B1b (<20%) produced by fermentation of streptomyces avermitilis. **Zhangx et al. (2006)**.

Sarcoptic mange mites are a tiny arachnids that are parasites of mammals causing mange infection and the mites which spend their life on their host causing various skin disorders of which variety are distributed world wide and many affect domestic and wild animals which includes pigs **Kutzer, (1989), foxes Scott, (2003), gorillas Graczyk et al., (2001)** and in Raccons **Suzuki et al., (1981)**. Mange is a most common and wide spread highly contagious disease of rabbits, it is found in various rabbit farms in Egypt. Mange frequently affect animals occurring in flock which kept under poor hygienic conditions,overcrowding, malnutrition, fatigue. Both Sarcoptic and Psoroptic mites are the causative agents of mange in rabbits **Soulsby, (1982)**. Sarcoptic mite burrows into the stratum corneum and feed on cells of stratum granulosum and stratum spinosum. Epidermal damage induces epithelial hyperplasia and the development of parakeratootic crust **Yager and Scott, (1993)**, fetal death may results if animals are untreated. Transitory infections may occur from various animals to humans and are spread by direct contact.

Ivermectin acts by blocking signal transmission from the ventral cord interneuron to the excitatory motor neurons through stimulation of inhibitory neurotransmitter gamma -aminobutric acid (GABA) from nerve terminals and potentiates GABA binding to the postsynaptic receptors, resulting in paralyzing and killing the parasite **Jacob et al., (1983)**.

Many trails were done by many workers to find out an effective remedy for controlling and getting rid of mange using various types of parentally and topically scabicides, but little is known about the control of mange by oral method .There are currently no licensed veterinary products specifically indicated for the therapy of ectoparasites in rabbits. A lack of licensed antiparasiticides for this indication in rabbits requires an off- label use of adequate pharmaceuticals. **Wilkins et al., (1980)** stated that a single subcutaneous injection of ivermectin 200 μg/kg body weight eliminated all Psoroptes cuniculi mites in rabbits. **Pandey, (1989)** in his study on ear mange mite of

rabbits used ivermectin subcutaneously with a single doses of 400 μg /kg body weight, diseased rabbits become negative from mites 6 days after treatment and remained so for a further 21 days. The incidence of adverse reproductive effects following clinical use of ivermectin is extremely low in all treated species (adverse reproductive effects include abortion, stillbirth, and infertility)in pregnant animals **Greene, (1991). Mc Keller et al., (1992)** administered ivermectin 400ug/kg b. wt. subcutaneously to infected rabbits with ear mite produced high and sustained concentrations in tissues and body fluid for at least 13 days. **Cutler, (1998)** used ivermectin injection successfully for treatment of ear and body mange of a pet rabbits. **EL-Shaieb** and **Mahmoud, (2000)** reported a significant increase in AST, ALT , and AP in rabbits injected ivermectin subcutaneously with 3 double therapeutic doses (0.4mg/kg. body weight) with one week intervals. **Magda and Fatma, (2003)** used Abamectin as a single dose of 200 μg/kg body weight subcutaneously against mites in both bucks and rams, resulted in clear improvement of infested areas without deleterious effects on biochemical parameters of treated animals. Sparsa et. al, (2006) used ivermectin (200μg /kg) orally in a single dose to treat scabies in humans, it was very effective, reports of adverse events are rare.

The aim of this work is to evaluate ivermectin oral formulation in treatment of rabbit mange as well as to follow up the incidence of adverse effects following clinical use, throw light on the clinical improvement and some serum biochemical panel and following up the treated rabbits.

MATERIALS AND METHODS

I- Drug : Ivermectin (Ivactin tablets , 6 mg each ,®)(Delta Pharma , tenth of Ramadan city , A.R.E.) was used in this study.

II-Animals: Twenty mixed-breed domestic rabbits were kept exclusively in cages indoors during the treatment period. Ages ranged from 6 month to 1 year with a mean age of 9 months. On Day 0, all animals were individually weighed. Body weight of the measured rabbits ranged from 2.1 to 3.7 kg with a mean body weight of 2.65 kg. Ten of them infected with sarcoptic mange. The infected animals were suffering from intense irritation of itching , scratching , appearance of areas denuded of hairs with scab formation, the other 10 rabbits were apparently clinically healthy.

Diseased rabbits were divided into 2 groups (each of five rabbits), the first group was served as non treated controls, while rabbits of the second group were given a single therapeutic dose of 400 μg /kg. b. wt. of ivermectin orally, taken in drinking water on empty stomach .

Healthy rabbits were also divided into 2 groups (each of five rabbits), the first group was control non treated, meanwhile the second was treated with ivermectin as a single orally dose of 400 μg /kg. b. wt., taken in drinking water on empty stomach .Results of treated rabbits were compared with untreated controls. No other treatment or environmental decontamination was performed during the trail. The success of the treatment was assessed by clinical as well as parasitological examination.

Clinical Examination: General health of all treated animals was observed daily, lesions were judged for each rabbit and observed side effects were recorded. Clinical signs were evaluated by scoring from absent (-), mild (+), moderately (++) or profoundly (+++) on days of 0, 7, 14 and 28 .

Parasitological Examination: On day 0,7,14 and 28 all rabbits were examined and epidermal debris was collected from infected areas for microscopic examination., epidermal debris and hairs were applied directly onto a microscope slide, covered with a few drops of mineral oil and a cover slip, then inspected at 40x magnification. **Soulsby, (1982)**. The safety of ivermectin was confirmed by investigations which are performed four weeks after administration of ivermectin, these investigations included some serum biochemical constituents.

Biochemical studies : blood sample was collected from the ear vein in test tubes, and left for clotting, then the serum was separated to assay of : Total proteins (TP), according to **Dumas, (1975)**; transaminase enzymes (AST & ALT) **Rittman and Frankel, (1957)**; alkaline phosphatase (ALP) **Kind and King, (1954)**; urea, **Fawcett** and **Scott, (1960);** creatinine, **Husdan and Raporpopt, (1968)** using Spectrophotometer (Spectrronic 20D, Milton Ray company) and kits(Bio-Adwic).

Periodic control to confirm healthy status of the rabbits, were carried out, and healthy status of the treated groups were observed. The obtained results were tabulated and statistical analysis, such as mean values, standard error and t. test were calculated according to **Petrie** and **Watson (1999)**.

RESULTS

Clinical signs of diseased rabbits conducting in sever pruritis with intense itching and loss of hair in the affected areas (lesions found on the fore and hind limbs near the nails) were the main characters found in most of the examined cases. In severely infected rabbits skin lesions were present on eye lids, nose, end of the tail and ears have been subsided by Day 7 in 4/5 rabbits and almost no signs of recurrence were apparent in the following weeks. All epidermal samples were negative by Days 28. No adverse reactions were observed.

Table (1) showed that lesions of (sarcoptic mites) began to disappear on the 7^{th} day post administration of ivermectin 400 μg /kg. b. wt. orally and all rabbits were curred completely on the 14^{th} day. the response to treatment was good. The control animals remained positive for mites through out the experiment

The study of the effect of antiparasitic drug (ivermectin) with therapeutic doses in liver and kidney functions resulted in decreased serum T P significantly and increased serum level of AST, ALT, ALP, while serum urea and creatinine were significantly higher in the treated groups relative to control. at four weeks post administration, (Table 2 and Table 3).

DISCUTION

Unhygienic conditions associated with malnutrition and overcrowding of animals are the main predisposing causes of mange infestation among animals. Moreover, environmental factors as climatic conditions and seasonal variations may favor the spread and propagation of the disease agents. Many insecticides which have shown promising results in the control of arthropods have been tested for the control of mange in rabbits and the lesions showed improvement but these insecticides required special safety precautions for human handlers and animals and these methods were stressful.

In this investigation, ivermectin at a dose of 400 μg /kg body weight once orally resulted in complete elimination of body mange in rabbits within 7 days, these results are in agreement with those obtained by **Wilkins et al., (1980); Pandey, (1989)** who found that ivermectin at 400 μg /kg. body weight subcutaneously as single dose resulted in complete cure of ear mange of rabbits, 6 days after treatment and remained so for a further 21 days. The result recorded in this investigation being similar to that obtained by **Werner** and **Matthes, (1989)** who treated scab leg in horses by ivermectin oral paste. at 200 μg /kg body weight and supported by **Radwan et al., (1987); Raisinghani et al., (1989); Magda** and **Fatma, (2003)**. This rapid action of ivermectin is due to partial paralysis or complete irreversible loss of ectoparasites motility **Centurier** and **Barth, (1980); Jacob et al., (1983)**.

Serum protein level was significantly decreased at 28 days post administration of ivermectin. The same results were recorded by **Ghoniem** and **Mansour, (1992); Emam** and **Abdella, (2000)** after using ivermectin in rabbits; **Magda** and **Fatma, (2003)** after using abamectin in rams and bucks. Hypoproteinaemia may be due to the destructive and toxic effect of ivermectin on the hepatocytes and renal epithelium **Ali et al., (1988)**.

Liver function was negatively affected, which was monitored by increasing the transaminase enzymes (AST& ALT) and ALP enzyme after 28 days of treatment, this results were consistent with those reported by **Ali et al., (1988); Goniem** and **mansour, (1992); EL-Shaieb** and **Mahmoud, (2000)** and **Emam & Abdella, (2000)**. The increased activities of AST, ALT and ALP indicate pathophysiological changes of the liver parenchyma for a certain period up to 28 days after injection. **Slantna et al . (1989)** found that liver contained the highest and most persistent residues of ivermectin .

It was demonstrated that ivermectin affected the renal function, so serum urea and creatinine levels were significantly increased after 28 days. **Shehata, (1995)** recorded that ivermectin at a dose of 0.2 mg/kg. b. wt. induced some degenerative changes of the tubular epithelium, glomerular capsular oedema and interstitial nephritis. Our results were disagreement with that obtained by **Magda and Fatma, (2003)** who recorded that abamectin alleviated the serum enzyme changes produced by mites toward the normal levels. **Emam and Abdella, (2000)** recorded that the toxic effects of ivermectin on liver and kidney function were transient and the treated ani-

mals required not less than 3 months after injection of ivermectin to regain their normality.

We concluded that simple dosing protocol used here , with an oral formulation administration, facilitates owner compliance with the treatment protocol. Other applications are more much time-consuming and laborious than oral administration.

Table (1): Clinical Efficacy of ivermectin Against Naturally Acquired infestation by sarcoptic mange in Rabbits: Clinical Signs of Mite infestation Before and After Treatment.

Clinical Signs	Number of Rabbits With Particular Scaling/Crusting(+,++,+++)			
	Day 0	Day 7	Day 14	Day 28
Scaling/crusting				
Absent(-)	-	4	5	5
Mild(+)	3	1	-	-
Moderate(++)	2	-	-	-
Profound(+++)	-	-	-	-
Clinical efficacy(%)	0(0/5)	80(4/5)	100(5/5)	100(5/5)

Table (2): The effect of ivermectin; 400 µg /kg body weight orally on some serum biochemical constituents at 4 weeks post administration in healthy rabbits. (n = 5).

Group / Estimated serum parameter	Non infected(non medicated) control X ± S . E .	Non infected(medicated) X ± S . E
Total protein (gm/dl)	7.12 ± 0.216	4.98 ± 0.216**
AST(IU/L)	38.2 ± 0.40	46.8 ± 1.073***
ALT(IU/L)	60.6 ± 0.724	73.2 ± 2.57**
ALP(U/100ml)	14.2 ± 0.112	22.0 ± 1.278**
Creatinine (mg/dL)	1.6 ± 0.107	1.98 ± 0.087*
UREA(mg/100dL)	23.8 ± 0.148	5.4 ± 1.675***

n = number of rabbits * P < 0.05 ** P < 0.01 *** P < 0.001

Table (3): the effect of ivermectin ; 400 µg /kg body weigh orally on some serum biochemical constituents at 4 weeks post administration in diseased rabbits with mange .

Group / Estimated serum parameter	Infected (non-medicated) control X ± S . E .	Infected (medicated) X ± S . E.
Total protein (gm/dl)	6.00 ± 0.323	4.80 ± 0.304*
AST(IU/L)	45.60 ± 1.572	52.64 ± 0.971*
ALT(IU/L)	69.20 ± 2.463	80.20 ± 1.727*
ALP(U/100ml)	19.2 ± 1.188	25.00 ± 1.572*
Creatinine(mg/dL)	1.9 ± 0.109	2.60 ± 0.15*
UREA(mg/100dL)	34.8 ± 2.826	44.6 ± 2.028*

n = number of rabbits * P < 0.05 ** P < 0.01 *** P < 0.001

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