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SOME HEMATOLOGICAL AND BIOCHEMICAL ALTERATIONS CONSEQUENT TO CONCURRENT ADMINISTRATION OF IVERMECTIN AND RAFOXANIDE IN RAMS

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ABSTRACT

Ivermectin and Rafoxanide are widely used in sheep as endoectoparasiticidal and fasciolicidal drugs. The effects of ivermectin and rafoxanide as well as their concurrent use as prophylactic drugs on hematological and serum biochemical parameters were studied in 20 apparently clinically healthy rams, classified into 4 equal groups . The 1st group was left without treatment (control). The 2nd group was injected s/c with ivermectin (0.2 mg kg-1) .The 3rd group was injected s/c with rafoxanide (3 mg kg-1). While, the 4th group was injected s/c with both drugs (0.2 mg ivermectin and 3 mg rafoxanide kg-1). Blood samples were collected weekly for 2 weeks for hematological and biochemical studies. The obtained results with ivermectin treated group revealed, a significant decrease in erythrocytic count, PCV % and Hb concentration,MCV and MCHC% . Meanwhile, significant increase in serum AST and ALT activities was recorded. The rafoxanide treated group provoked a significant decrease in leuckocytic and erythrocytic counts, Hb%, PCV%, MCV, MCH and MCHC% as well as serum triglycerides level. Mean while, a significant increase in serum cholesterol and LDL-c levels was reported.Moreover, the group treated S/C with both drugs, elicited a significant decrease in erythrocytic and leukocytic

counts, PCV%, MCV, MCH, MCHC%, triglyceride levels and Hb%. In contrast, a significant increase in AST, ALT activities, cholesterol and LDL-c levels was recorded. While, in comparison with ivermectin and rafoxanide treated groups, there was insignificant changes in albumin, blood urea nitrogen, creatinine, HDL-c and erythrocytic count. In opposite side, there was a significant increase in serum AST, ALT and LDL-c levels as compared with ivermictin and rafoxanide treated groups. Also, there was a significant decrease in Hb%, PCV%, MCV,MCH and MCHC%. Meanwhile, a significant increase in serum cholesterol level as compared with ivermectin treated group. Moreover, there was insignificant changes in serum cholesterol and triglyceride levels, erythrocytic count, Hb%, PCV%, MCH and MCHC% as compared with rafoxanide treated group. In conclusion it could be concluded that hematological and biochemical alterations obtained with concurrent administration of both ivermectin and rafoxanide didn't differ greatly than those obtained with each of them when injected alone and there is no additional dangerous from this combination.

INTRODUCTION

Anthelmintics are widely used for combating or treating different helminthes infections of different animal species. Chemotherapy of parasitic infestations with a wide spectrum of activity and minimal side effects are the main objects. Ivermectin, a potent broad spectrum antiparasitic drug from macrocyclic lactone family ***(Lespine et al.,2006)*** is a mixture of two natural fermentation products of *Streptomyces avermitilis.*It is a 22,23-dihydroivermectin B_{1a} and is usually marketed as a mixture of 22,23-dihydroivermectin B_{1a}(> 80%) and 22,23-dihydroivermectin B_{1b} ***(Mackellar and Benchaoui, 1996)***. The drug

exerts its toxic action by blocking the excitatory motor neurons in parasites which contain Gamma Amino Butyric Acid (GABA) in their nervous system ***(Leaning, 1981 and Barragry, 1987)***. Consequently, nematodes and arthropods that rely on GABA-mediated neural transmission are affected, while cestodes and trematodes which do not rely on GABA-mediated neural transmission are `not affected ***(Egerton et al., 1980*** and ***Campbell et al., 1963)*** Moreover; the drug has ovicidal as well as larvicidal effects ***(Anantaphruti et al., 1982)***. In sheep and goats ivermectin is highly effective against all the important pathogenic gastrointestinal nematodes, lung nematodes, nasal bots and mites ***(Mackellar and Benchaoui, 1996)*** nevertheless, the extremely potent antiparasitic activity of ivermectin is greatly averted by its frequently encountered adverse effects. Detailed studies divulged hepatitis in goats ***(Ali and Abu-Samra, 1987)*** and altered hepatic function in rams ***(Hassan et al., 1995)*** in response to ivermectin treatment. The previous side effects could represent a crimp in substantially efficient use of this drug in these species. Rafoxanide is a member of halogenated alicylanilides with potent antiparasitic activity. It has the chemical formula [3́-chloro-4´ (p-chlorophenoxy)-3, 5 diiodosalicylanilide] ***(Adams, 1995)***. It is a widely used in sheep as a fasciolicidal drug. It is used for the control of *Fasciola spp, Haemonchus spp* ***(Swan, 1999)*** *and Oestus ovis* ***(Sanyal et al., 1986 and Swan, 1999)*** infestations in sheep in many parts of the world. Its fasciolicidal effect in sheep depends on the persistence of the drug in plasma. It is extensively bound to plasma protein and has a long half life about (16.6 day) as reported by ***Barragry, (1994)***. The mechanism of action of salicylanilides and their substituted phenol is through their action as uncoupler of oxidative phosphorylation

(Adams, 1995). The drug is more effective on adult than immature flukes ***(Richard et al., 1990)***. Both ivermectin and rafoxanide are commonly concurrently used for prophylaxis and treatment of nematodes, external parasites and Fasciola infestations in sheep and there is no available data concerning the untoward effects of their concurrent use. In support of the previous concept, the present study was designed to unearth the possible side effects of ivermectin, rafoxanide and their concurrent use as prophylactic drugs that would be portrayed as undesirable biochemical and hematological effects.

MATERIAL AND METHODS

1-Drugs:

A- (Ivermectin 1%) ® is produced by Kahira Pharmaceutical and Chemical Industries Company, Cairo, Egypt. The drug is available as injectable 1%, w/v sterile solution. The drug was administered subcutaneously as a single dose of o.2 mg kg^{-1} ***(Garg et al., 2007).***

B- (Rafoxanide) ® is produced by the Egyptian Company for Chemical and Pharmaceuticals (ADWIA), the drug is available as injectable solution 7.5% each vials contains 1oo ml. This drug was administered as single dose of 3mg kg^{-1} ***(Adams, 1995).***

2-Animal:

The present study was carried out on 2o apparently clinically healthy rams 40-50 kg. They were housed in open yard system and fed on dry ration and barseem *ad-libitum*. Rams were classified into 4 equal groups . The 1st group was left without treatment (control). The 2nd group was injected subcutaneously with ivermectin in a dose of o.2 mg / kg^{-1}

(ivermectin treated group). The 3rd group was injected subcutaneously with rafoxanide in a dosage of 3 mg kg^{-1} (rafoxanide treated group). The 4th group was injected concurrently subcutaneously with both drugs o.2 mg kg^{-1} (ivermectin) and 3 mg kg^{-1} (rafoxanide) (ivermectin and rafoxanide treated group).

3-Sampling:

Two blood samples were collected by jagular puncture from animals after one and two weeks post drugs administration. The 1st sample was collected in centrifuge tube without anticoagulant and used for separation of clear serum for biochemical analysis. The serum was separated by centrifugation at 300 r.p.m. for 15 minutes and kept frozen at – 20 ˚C till assayed. The 2nd sample was collected in a test tube containing EDTA as anticoagulant and used for hematological studies.

4-Analysis:

A- Biochemical analysis:-

The serum samples were used for determination of triglycerides ***(Bucolo and David, 1973)***, total cholesterol ***(Mellattini, 1978),*** HDL-c ***(Clark et al., 1983),*** LDL-c ***(Friedwald et al., 1972),*** Albumin **(Gassbaro et al., 1972),** blood urea nitrogen ***(Putton and Crouched, 1977),*** creatinine ***(Young et al., 1975)*** and serum AST and ALT levels ***(Reitman and Frankel, 1977)***.

B- Hematological analysis:-

The hematological parameters (Hb%, RBCs and WBCs counts and PCV %) were determined according to **(Dacie and Lewis, 1994)**. Blood indices were calculated using these equations:

- Mean Cell Volume (MCV) = PCV %/RBCs x 10^6 X 10 fl

- Mean Cell Hemoglobin (MCH) = Hb g/dl/RBCs x 10^6 X 10pg/cell

- Mean Cell Hemoglobin Concentration (MCHC) = Hb g/dl / PCV %X100 g/dl

C- Statistical analysis:-

The results were reported as the mean ± S.E. Statistical significance was determined using analysis of variance according to ***(Snedcor and Cochran, 1982)*.** Means were compared by Least Significance Difference (LSD) test at 0.5 significance level ***(Steel and Torrie, 1980)*.**

RESULTS AND DISCUSSION

Hematological findings:

Concerning the effect of s/c administration of ivermectin, rafoxanide and their concurrent use on hemogram (Table 1) and hematological indices (Table 2) of treated rams, it was indicated that, s/c injection of ivermectin (0.2 mg kg^{-1}) evoked non significant change in leukocytic count (after 1st and 2nd weeks) . On other side, there was a significant decrease in erythrocytic count PCV % and Hb% (after 1st and 2nd weeks) . The hematological indices revealed significant decrease in MCH, MCHC and MCV values (after 1st and 2nd weeks).It was cleared that, s/c administration of rafoxanide (3mg kg^{-1}) elicited significant decrease in leukocytic and erythrocytic counts, Hb concentration and PCV % (after 1st and 2nd weeks). The hematological indices emphasized a significant decrease in MCH , MCHC and MCV values (after 1st and 2nd weeks). Regarding the effect of concurrent s/c administration of both ivermectin (0.2 kg^{-1}) and rafoxanide (3mg kg^{-1}), it was found that there was significant decrease in leukocytic and erythrocytic counts, PCV % and Hb%(after 1st and 2nd weeks) as well as Hb concentration (after 1st

week) as compared with the control group. While, in comparison with ivermectin and rafoxanide treated groups, there was a significant decreasee in RBCs count (after 1st and 2nd weeks)as compared with ivermectin and rafoxanide treated group as well as a significant decrease in Hb concentration (after 1 st week) and PCV% (after 1st and 2nd weeks) as compared with ivermectin treated group.In contrast,there was non significant change in erythrocytic count , Hb% and PCV%(after 1st and 2nd weeks) as compared with rafoxanidetreated group. The hematological indices provoked significant decrease in MCH, MCHC, andMCV values (after 1st and 2nd weeks)while, in comparison with ivermectin treated group, In contrast,there was non significant change in MCH and MCHC% (after 1st and 2nd weeks) as compared with rafoxanide treated group.

Analysis of the hematological parameters can be beneficial in assessing animal health as the hemogram and blood indices reflect the statement of the animals. From these obtained results, it was evident that s/c administration of ivermectin, rafoxanide and their concurrent use decreases the erythrocytic count and Hb level of treated rams. Unfortunately, our findings can not provide us with a ready explanation for ivermectin induced anemia in treated rams. It is worthwhile to contemplate proposals that enlighten us with a proper explanation. The anemia may be due to alteration of haematopoiesis as a result of hepatic pathological lesions or might be due to reduction in bile salts in small intestine since bile acids are necessary for reduction of ferric ions to ferrous easily absorbed ***(Kaneko et al., 1997)***. In the glow of the previous notion one could attribute this ivermectin induced anemia to inhibition of haemopoiesis caused by hepatic pathological lesions. This suggestion confirmed by ***Roey et al., (1992)***, ***Zaied (1995)***, ***Wanis (1996)*** and ***Gad***

(1998) and ***Zaied (2004)***. The authors stated that therapeutic dose of ivermectin induced various hepatic degenerative changes, cloudy swelling lymphocytic infiltration, coagulative necrosis and congestion of hepatic blood sinusoids. Moreover, this suggestion is further confirmed by Ali and ***Abu-Samra (1987)*** who reported that ivermectin treatment induced hepatitis in goats. On other side, these results are incompatible with that recorded by ***Asquith (1981)*** who stated that, i.m injection of ivermectin to adult horses at 0.2 or 0.3 mg kg^{-1} revealed no changes in hematological values. Also, these results were in disagreement with that reported by ***Berm and Bulman (1986)*** who recorded that the hematological values of cattle treated s/c with ivermectin at 0.2 mg kg^{-1} three times with 30 days intervals showed little or no effect at 1 and 7 day after each of three treatments. These data were also, incompatible with that detected by ***Mahzunlar (1989)*** and ***Nakai (1990)*** who found that dogs treated with ivermectin revealed no abnormalities for any variable measured at hematological examination. Also, these results were disagree with ***Roy et al., (1992)*** who showed that s/c treatment of 4 clinically healthy female goats with ivermectin at a dose of 0.2 mg kg^{-1} for 7 consecutive days revealed non significant changes in Hb levels, total erythrocytic count, total and differential leukocytic counts and blood clotting time. Moreover, these data were not coincided with Ragab (1994) who stated that, ivermectin injection 0.2 mg / kg^{-1} for 7 days in did not produce any untoward effects on Hb, RBCs, total and differential leukocytic counts. Additionally the results were in disagreement with those recorded by **Wanis (1996)** and who noted that male rats injected s/c with ivomec-f and ivermectin in dose of 0.2 and 0.3 mg / kg^{-1} respectively, reflected insignificant changes on erythrocytic and leukocytic counts, PCV% and Hb concentration along the course of the experiment.

Concern regarding Rafoxanide induced anemia, our findings were nearly fit with ***El-Sayed and El-Sayed (2000)*** who reported that s/c treatment of ewes with rafoxanide at 3 mg kg-1, induced reduction in Hb concentration (after 1st week) and leukocytic and erythrocytic counts (after 2nd week). Concerning anemia induced by concurrent use of both drugs, undoubtedly our findings obtained with other two treated groups provide us with a ready explanation and needless to say this could be attributed to augmented effect of both drugs.]

Biochemical findings :

The results concerning tested serum parameters are summarized in Table (3). It was cleared that, s/c administration of ivermectin induced significant elevation in serum AST (after 2nd week) and serum ALT (after 1st and 2nd weeks). Undoubtedly, our findings fit in with those reported by ***Roey et al., (1992)*** who found that s/c administration of ivermectin (0.2mg $^{kg-1}$) to 4 clinically healthy female goats for 7 consecutive days elicited an increase in serum AST and ALT levels. These results were also in accordance with ***Ragab (1994)*** who noted that female sheep injected with ivermectin (0.2 mg kg^{-1} for 7 consecutive days produced a significant increase in serum transaminases level. Moreover these results were also go parallel with ***Hassan et al., (1995), Zaied (1995)*** and ***Wanis (1996)*** and ***Zaied (2004)***. On other side, these data were in disagreement with that reported by ***Asquith and Kulwich (1981), Brem*** and ***Bulman (1986)*** and ***Uysal and Mahzunlar (1989)***. Also, s/c administration of ivermectin revealed non significant change in albumin, blood urea nitrogen, creatinine, cholesterol, triglycerides, HDL-c and LDL-c. Our results are in harmony with ***Asquith and Kulwich (1981), Brem and Bulman (1986), Nakai et al., (1990), Wanis (1996)*** *and* ***Zaied (2004).***

Regarding the effect of rafoxanide treatment, it was emphasized that, s/c administration of rafoxanide (3mg kg^{-1}) provoked a significant increase in serum AST and ALT levels as compared with the control. Serum transaminases including AST and ALT are found in most tissues but in equal proportions. ALT occurs exclusively in the liver, but only in the cytoplasm of parenchymal cells, in contrast to AST which is equally distributed between the cytoplasm and mitochondria. ***Doxy (1971)*** stated that the level of these enzymes is increased following liver damage. Accordingly, could attribute an elevation of AST levels to the damage of hepatic cells by direct effect of the drug resulting escape of these enzymes to the plasmas. On other side, our findings were in disagreement with ***El-Sayed and El-Sayed (2000)*** who found that there was non significant change in ALT following s/c administration of rafoxanide to ewes. The present results were also in disagreement with ***Bulent et al., (2006)*** who recorded that there was non significant change in AST following oral administration of rafoxanide to cattle. Rafoxanide treatment also revealed non significant change in albumin, blood urea nitrogen, creatinine and HDL-c. These results were nearly correlate with ***Swan and Schroder (1981)*** and ***Shroder (1982)*** who stated that rafoxanide is save in sheep and cattle when administered at the recommended therapeutic dose. Also, these findings were coincided with ***Adams (1995)*** who concluded that the therapeutic dose of rafoxanide is save in cattle and sheep of all ages without any hazards. Moreover, these results were nearly similar to those obtained by ***El-Sayed and El-Sayed (2000)***. The s/c administration of rafoxanide to rams also elicited a significant increase cholesterol and LDL-c levels, meanwhile significant

decrease in triglycerides level (after 1st and 2nd weeks). Our data confirmed by ***El-Sayed and El-Sayed (2000)*** who concluded that s/c administration of rafoxanide to ewes produced an elevation in total cholesterol (after 2nd week) and LDL-c (after 1st and 2nd week) levels. The concurrent injection of both ivermectin (0.2mg $^{kg-1}$) and Rafoxanide (3mg kg^{-1}) provoked a significant increase in serum AST and ALT levels as compared with control, ivermectin and rafoxanide treated groups. This elevation might conceivable to be due to the effect of both drugs. This suggestion was confirmed by obtained data with ivermectin and rafoxanide treated groups in this study. Also, rams treated s/c with both ivermectin (0.2mg^{kg-1}) and rafoxanide (3mg kg^{-1}) concurrently showed non significant changes in albumin, blood urea nitrogen, creatinine and HDL-c levels (after 1st and 2nd weeks) as compared with control, ivermectin and rafoxanide treated groups. Undoubtedly, our findings obtained with ivermectin and rafoxanide treated groups provide us with a ready explanation and needless to say these results coincided with that recorded by ***Asquill and Kulwish (1981), Berm and Bulman (1986), Naka et al., (1990), Poul et al., (1993), Adams (1995) and El-Sayed and El-Sayed (2000)*** who concluded that both drugs are safe drugs. Moreover, rams treated s/c with ivermectin and rafoxanide concurrently indicated a significant decrease in serum triglycerides level as compared control and ivermectin (after 1st and 2nd weeks) as well as rafoxanide (after 2nd week) treated groups. This effect could be attributed to rafoxanide as obtained in this study and confirmed by ***El-Sayed and El-Sayed (2000).***

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بعض التغيرات الدمويه والبيوكيميائيه الناتجة عن الاستخدام المتزامن للأيفرميكتين والرافوكسانيد في الكباش

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يستخدم كلا من الأيفرميكتين و الرافوكسانيد على نطاق واسع لعلاج الطفيليات الخارجية والديدان الداخلية و الفشيولا في الأغنام. أجريت هذه الدراسة على عدد 20 من الكباش البالغة السليمة ظاهريا وذلك لمعرفة بعض التغيرات الدموية والكيميائية الناتجة عن استخدام كلا من هذين العقارين على حده وكذلك استخدامهما لمتزامن. قسمت هذه الكباش إلى أربعة مجموعات متساوية قوام كل مجموعة خمسة

أفراد. المجموعة الأولى تركت بدون أي علاجات كمجموعة ضابطة. المجموعة الثانية تم حقنها تحت الجلد بعقار الأيفرميكتين بالجرعة العلاجية (0.2مجم / كجم وزن حي). المجموعة الثالثة تم حقنها تحت الجلد بعقار الرافوكسانيد بالجرعة العلاجية (3مجم / كجم وزن حي). المجموعة الرابعة تم حقنها تحت الجلد بكلا العقارين معا وفى نفس التوقيت و بنفس الجرعات سابقة الذكر. تم تجميع عينات دم من الوريد الوداجى وذلك بعد أسبوع وكذلك بعد أسبوعين من الحقن وذلك لمعرفة التأثير على صورة الدم وكذلك المكونات البيوكيميائية لمصل الدم.

وقد أظهرت النتائج المتحصل عليها نتيجة حقن الأيفرميكتين تحت الجلد حدوث نقص معنوي في عدد كريات الدم الحمراء, حجم الكريات المرصوصة، الهيموجلوبين ومتوسط هيموجلوبين الخلية،و متوسط تركيز هيموجلوبين الخلية بينما أظهرت نفس المجموعة حدوث زيادة معنوية فى مستوى أنزيمات الألانيين و الاسبرتيت ترانسفيريزس.

كما أظهرت المجموعة المعالجة الرافوكسانيد حدوث نقصا معنويا في عدد كريات الدم الحمراء و البيضاء, نسبة الهيموجلوبين, حجم الكريات المرصوصة, متوسط حجم الكريات ومتوسط هيموجلوبين الخلية ومتوسط تركيز هيموجلوبين الخلية كذلك مستويات الدهون الثلاثية بمصل الدم بينما أظهرت نفس المجموعة حدوث زيادة معنوية في مستويات الكوليسترول و الدهون منخفضة الكثافة مقارنة بالمجموعة الضابطة.

و قد أظهرت المجموعة المحقونة بكلا العقارين في نفس الوقت حدوث نقص معنوي في عدد كريات الدم الحمراء و البيضاء, حجم الكريات المرصوصة , متوسط حجم الكريات و الدهون الثلاثيه و الهيموجلوبين مقارنة بالمجموعة الضابطة, على الجانب الآخر كان هناك زيادة معنوية في حجم هيموجلوبين الخلية متوسط تركيز هيموجلوبين الخلية و كذلك مستويات أنزيمات الألانيين و الاسبرتيت ترانسفيريزس , الكولسترول و الدهون منخفضة الكثافة بمصل الدم مقارنة بالمجموعة الضابطة.

و في مقارنة بالمجموعات المعالجة الأخرى أظهرت هذه المجموعة عدم حدوث أي تغير معنوي في مقارنة بالمجموعات المعالجة الأخرى أظهرت هذه المجموعة عدم حدوث أى تغييرات معنوية فى قيم

مستويات الزلال، اليوريا، الكرياتنين، الدهون عالية الكثافة وعدد كريات الدم الحمراء. على الجانب الآخر كانت هناك زيادة معنوية فى مستويات أنزيمات الألاتين والأسبرتيت ترايسفيرير، الكولستيرول والدهون منخفضة الكثافة بمصل الدم مقارنة بكل من المجموعة المعالجة بالأيفرميكتين وكذلك المجموعة المعالجة بالرانوكسابيد.

وبالمقارنة بالمجموعة المعالجة بالأيفرفكسين كان هناك نقص معنوى فى نسبة الهيموجلوبين، حجم الكريات المرصوصة، متوسط حجم كريات الدم، متوسط هيموجلوبين الخلية ومتوسط تركيز هيموجلوبين الخلية. وفى المقابل كانت هناك زيادة معنوية فى مستوى الكولستيرول بمصل الدم. وبمقارنة هذه المجموعة مع المجموعة المعالجة بالراموكسانيد لم يكن هناك أى تغييرات معنوية فى مستويات الكولستيرول والدهون الثلاثية بمصل الدم، عدد كريات الدم الحمراء، نسبة الهيموجلوبين، حجم الكريات المرصوصة، متوسط هيموجلوبين الخلية ومتوسط تركيز هيموجلوبين الخلية.

و قد خلصت هذه الدراسة إلى أن التغيرات الدموية و البيوكيميائية الناشئة عن الحقن المتزامن بكلا من عقاري الأيفرميكتين و الرافوكسانيد لا تختلف عن تلك التي نتجت عن حقن كلا من العقارين على حده , و بناء عليه لا توجد خطورة مضاعفة من ذلك الاستخدام.