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Immunological and Biochemical Profiles of Tilmicosin in Rabbits

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Abstract

This study aimed to evaluate the effect of tilmicosin on rabbit immunity after daily subcutaneous (S.C) injection for 3 successive days. Fifteen New Zealand male rabbits were divided into 3 groups; the first group was left as a control, the second was non treated vaccinated against pasteurellosis (1 mL S.C in the skin fold of the back of the rabbit), while, the third was vaccinated and treated by tilmicosin in a dose of 10 mg/kg BW daily for 3 days. Whole blood and serum samples were collected from each rabbit on 1st ,3rd ,9th ,14th ,21st and 28th days post drug administration to determine some immunological and biochemical parameters. Histopathological examination of liver, kidneys and heart of all groups was also carried out. The results revealed that tilmicosin elicited a significant increase in B-lymphocytes, nitric oxide production by macrophages and lysozyme activity of the serum. Meanwhile, the drug had no significant changes on alanine aminotransferase enzyme (ALT) and aspartate aminotransferase enzyme (AST) levels (liver enzymes). On the 21st day ALT showed significant decrease. Moreover; there were no significant changes on urea and creatinine levels (kidney functions) when compared with control group. Histopathological findings of the vaccinated and treated groups showed lesion score from 1st and 2nd degree. It could be concluded that tilmicosin afforded a good effect on rabbits' immunity without negative effects on liver and kidney functions.

Keywords: Tilmicosin, Pasteurollosis, New Zealand Rabbits, Lysozyme activity, Lymphocyte, liver enzymes.

Introduction

Since the use of chemotherapeutic agents was widely introduced in the veterinary field, many authors have studied their influence on the immune response against animal diseases. Nonspecific immune-stimulants are gaining increased attention and attraction for medication in the veterinary field through potentiation of the immune response to applied vaccines [1]. Immunosuppressive properties of some antibiotics are represented by inhibition of both cellular and humoral immune responses to a variety of vaccines [2].

Tilmicosin is one of the macrolide antibiotics developed for veterinary use. It is synthesized from tylosin, and has an antibacterial spectrum similar to tylosin with enhanced activity against *Pasteurella multocida* and *Pasteurella haemolitica* [3]. It acts by inhibiting protein synthesis by binding to the 50 S ribosomal subunit of sensitive microorganisms [4]. Tilmicosin is used for treating some diseases caused by tilmicosin sensitive microorganisms such as: respiratory tract infections in rabbits caused by *P. multocida* and *Bordetella bronchiseptica* as well as bacterial enteritis caused by clostridia. Moreover, *Mycoplasma gallisepticum* and *M. synoviae* are sensitive to tilmicosin [5,6]. The aim of this study was to investigate the immunological and biochemical effects of tilmicosin in rabbits vaccinated with *P. multocida*.

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Material and Methods

Animals and experimental design

Tilmicosin phosphate was obtained from (ELANCO Animal Health, Eli Lilly, Geneva, Switzerland) as an aqueous solution in dark plastic bottle containing 240 mL (250 mg/mL). The molecular formula is: $C_{46}H_{80}N_2O_{13}$ [7]. It was injected S.C with a dose of 10 mg/kg BW once daily for 3 successive days [8]. Formalinized killed *P. multocida* vaccine was obtained from Veterinary Serum and Vaccine Research Institute (VSVRI), Abassia, Cairo, Egypt. It was administrated S.C in a dose of 1 mL in the skin fold of the back of the rabbits [9]. Fifteen male New Zealand rabbits were divided into three equal groups each of five weighing about 1.5 kg/animal. Each rabbit was kept in a separate cage and fed dry pellets (150 g/rabbit twice daily). Animals in the 1st group were kept as control, they received no drug and no vaccine all over the experimental period. Those of the 2nd group were non treated vaccinated with formalinized killed *P. multocida* vaccine in a dose of 1 mL in the skin fold of the back of each animal. Rabbits in the 3rd group were S.C injected with tilmicosin (10 mg/kg BW) once daily for 3 successive days and then vaccinated with the same vaccine at the same day in which the 2nd group was vaccinated.

Heparinized blood samples (2 mL from the ear vein) were obtained on 1st, 3rd and 9th day post vaccination from the vaccinated group and treated vaccinated group for the application of lymphocyte transformation assay [10]. For estimation of liver and kidney function tests (ALT, AST, Urea and Creatinine) and measurement of nitric oxide produced by macrophages in the serum, 3 ml of blood were collected from each rabbit on 1st, 3rd, 9th, 14th, 21st, 28th days [11,12].

Histopathological changes of liver, kidneys and heart following tilmicosin medication were investigated at the end of the experiment (28th day). Two animals were sacrificed from each group and tissues were placed in 10% formalin solution then embedded in paraffin and stained by H&E [13].

Analytical procedures

Serum nitric oxide level was measured with colorimetric method using Griess reagent, while serum lysozyme activity was estimated according to Schltz [12]. Lymphocyte transformation test using MTT (3-{4,5-dimethylthiazol-2-yl}-2,5-diphenyltetrazolium bromide) which was used for separation of mononuclear cells. Reactivos GPL kits was used for estimation of liver functions (ALT, AST) according to Amador and Wacker [15] and Bergmeyer [16], respectively. Also, kidney function tests (blood urea nitrogen and creatinine) according to Tabacco [17] and Henry *et al*. [18], respectively, were carried out.

Statistical analysis

The data were analyzed using SPSS version 21, IBM Corp., Chicago, IL, USA. Analysis of variance (one –way ANOVA) was used to detect the differences between treatments. Data were expressed as mean ± SD and Duncan's test was used to find the differences among means. Results with $P \leq 0.05$ were considered significantly different.

Results

Immunological results

The data represented in the present study emphasized a significant increase in all the examined parameters (B-lymphocyte transformation test, nitric oxide test and lysozyme activity), when comparing the vaccinated treated and vaccinated non treated groups with control group on the 3rd and 9th days post vaccination. Moreover, there was a significant increase in lymphocyte transformation in vaccinated treated group compared with the vaccinated non treated one on 3rd and 9th day (Table 1).

Biochemical results

The obtained results indicated that there was a significant increase in AST activity in 1st day, 3rd day and 9th day of the experiment in the vaccinated and treated group compared with control group. In 14th, 21st and 28th days of the experiment there was no significant

changes in vaccinated, treated group compared with control group. In vaccinated non treated group, there were an increase in AST levels all over the period of experiment compared with control group, with more increase in 14th and 21st days than the others (Table 2).

There was a significant increase in the ALT activity in vaccinated and treated groups compared with the control group at 1st, 3rd and 9th day of the experiment. At 14th and 28th day, there were no significant changes in the ALT levels when compared with the control group. At 21st day, the results were at normal level. In vaccinated non treated group, there was significant increase in the ALT levels at 1st, 3rd, 9th, 14th and 21st days of the experiment when compared with control group. At 28th day of the experiment, there was no significant changes in the ALT level when compared with control group (Table 2).

Our results demonstrated a significant increase in serum creatinine level at 1st, 3rd and 9th days of the experiment in vaccinated and treated group when compared with control group. At 14th, 21st and 28th days, there were no significant changes in the serum creatinine levels in vaccinated and treated groups compared with the control group. In vaccinated non treated group, there were no significant changes in the serum creatinine level all over the experimental period compared with the control group (Table 2).

Table 1: The effect of tilmicosin treatment (10 mg/kg BW/day S.C) for 3 successive days and formalinized killed *P. multocida* vaccine (1 mL S.C in the skin fold in the back of the New Zealand rabbit) on humoral immunity parameters

Groups	Lymphocyte transformation			Serum nitric oxide (ng/mL)			Lysozyme activity (µg/mL)		
	1st day	3rd day	9th day	1st day	3rdday	9thday	1st day	3rdday	9thday
Control	0.5±0.03[a]	0.64±0.28[c]	0.58±0.01[c]	7.3±0.3[a]	9.8±1.2[b]	10.04±0.96[c]	184.6±5.4[b]	183.6±6.2[c]	163.3±5.9[c]
Vaccinated non treated	0.64±0.03[a]	0.88±0.02[b]	0.98±0.71[b]	6.3±0.8[a]	10.7±1.3[b]	25.1±1.8[b]	180.6±6.7[b]	248.4±4.67[b]	266.8±3.5[b]
Vaccinated treated	0.599±0.03[a]	1.32±0.29[a]	2.35±0.5[a]	6.8±0.62[a]	40.3±1.4[a]	53.4±2.1[a]	200.2±3.3[a]	279.5±3.5[a]	288.3±4.4[a]

Means within the same column carrying different superscripts are significant at ($P \leq 0.05$).

The results of this study demonstrated a significant increase in serum urea level at 1st, 3rd, 9th and 14th days of the experiment in vaccinated and treated groups compared with the control group. At 21st and 28th days of the experiment, there were no significant changes in the serum urea level in vaccinated and treated group compared with the control group. In vaccinated non treated group, there was significant increase in the serum urea level all over the period of the experiment compared with the control group (Table 2).

Table 2: The effect of tilmicosin treatment (10 mg/kg BW/day S.C.) for 3 successive days and formalinized killed *P. multocida* vaccine (1 mL in the skin fold in the back of the New Zealand rabbit) on liver enzymes and kidney parameters

		Control	Vaccinated non treated	Vaccinated treated
AST(U/L)	**1st day**	15.2±0.08^{c}	19.2±0.8^{b}	25.4±0.05^{a}
	3rd day	15.4±0.054^{c}	19.8±0.83^{b}	27± 1.0^{a}
	9th day	15.4±0.054^{c}	19.6±0.54^{b}	25.4±0.54^{a}
	14th day	15.8±0.83^{b}	20.8±0.83^{a}	18.8±1.09^{a}
	21st day	15.8±0.83^{c}	20±1.22^{a}	17.8±2.04^{b}
	28th day	16± 1.0^{b}	19.4±0.54^{a}	18.8±1.09^{ab}
ALT(U/L)	**1st day**	9.0 ± 1.0^{c}	12.6 ±1.67^{b}	23.4±0.54^{a}
	3rd day	8.8 ±0.83^{c}	13.8 ±0.83^{b}	23.6 ±0.89^{a}
	9th day	10.6±0.54^{c}	13.8±1.09^{b}	23.8±0.83^{a}
	14th day	9.6±0.54^{b}	13.8±0.84^{a}	11.8±1.09^{ab}
	21st day	11.4±0.54^{b}	13±1.22^{a}	10.6±0.54^{b}
	28th day	8.8±0.83^{b}	10.8±0.83^{a}	10.8±1.09^{a}
Serum Creatinine(mg/dl)	**1st day**	0.42±0.027^{c}	0.54±0.05^{b}	0.84 ± 0.054^{a}
	3rd day	0.45±0.057^{c}	0.55±0.057^{b}	0.85± 0.057^{a}
	9th day	0.45±0.057^{c}	0.55 ±0.057^{b}	0.75 ±0.057^{a}
	14th day	0.42±0.027^{c}	0.56±0.054^{b}	0.62 ± 0.016^{a}
	21st day	0.42±0.027^{c}	0.58±0.083^{a}	0.54 ± 0.054^{b}
	28th day	0.44±0.054^{c}	0.56 ±0.054^{a}	0.46 ± 0.054 ^{b}
Serum Urea(mg/dl)	**1st day**	15.6 ±0.54^{c}	19.8 ±1.095^{b}	33±2.73 ^{a}
	3rd day	16.2±0.83^{c}	20.6 ±0.54^{b}	26.6 ±1.51^{a}
	9th day	15.6 ±0.54^{c}	20.6 ±0.54^{b}	28.0±1.22^{a}
	14th day	16.0± 1$^{.0c}$	21.8 ±0.83^{b}	22.2±2.58^{a}
	21st day	16.4 ±1.34^{b}	20.8 ±0.83^{a}	17.8 ±2.04^{b}
	28th day	16.4 ±1.34^{b}	20.8 ±1.095^{a}	17.6 ±0.54^{b}

Means within the same row carrying different superscripts are significant at ($P \leq 0.05$).

Histopathological results

In vaccinated non treated and vaccinated, treated groups, the histopathological changes in liver, kidneys and heart were illustrated in Figure (1).

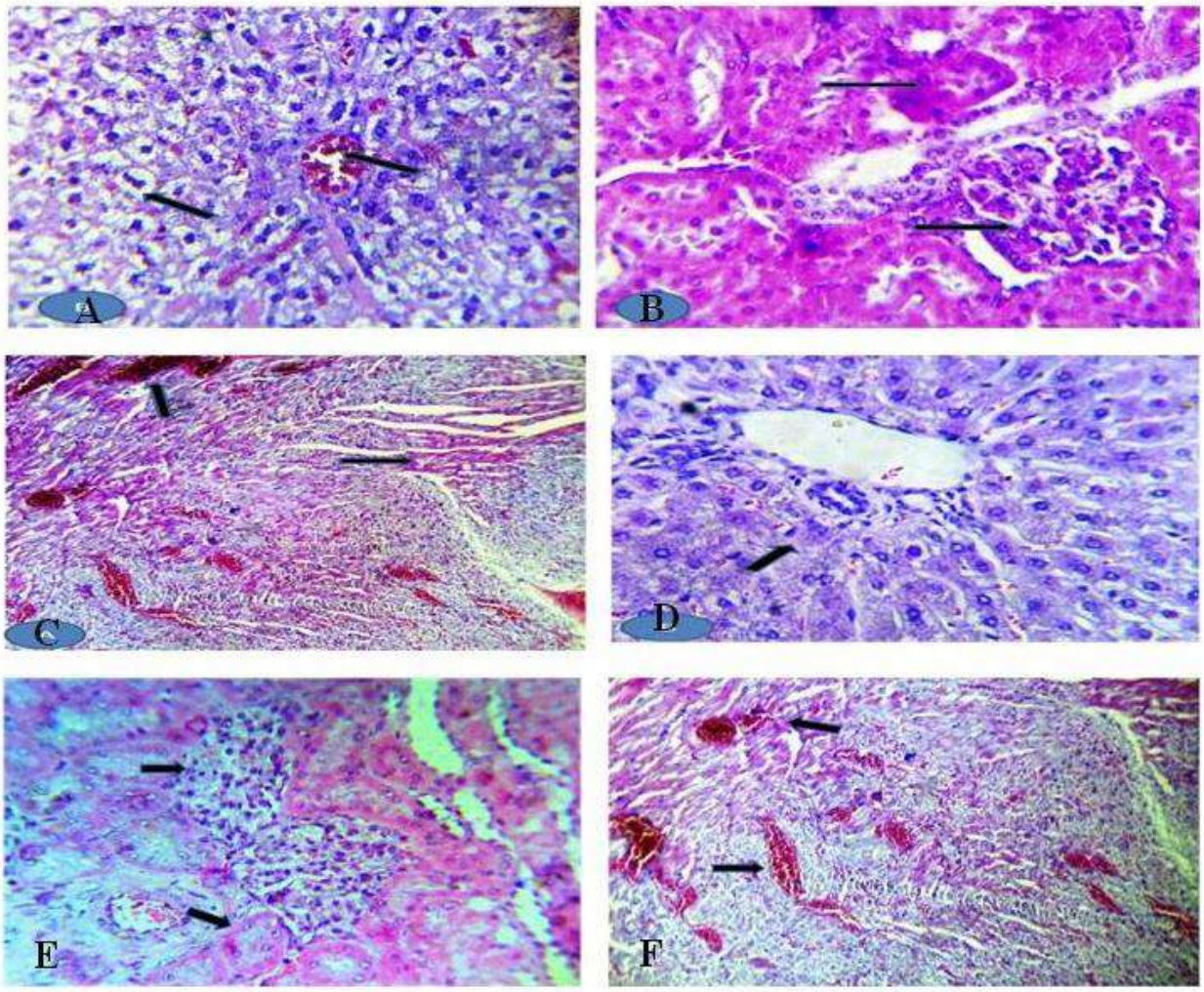

Figure 1: Histopathological changes in liver, kidneys and heart tissues of NewZeland rabbits vaccinated and/or treated with *P. multocida* and Tilmicosin, respectively. (A: Liver of vaccinated non treated animals showing moderate congestion of hepatic blood vessels and sinusoids and hydropic degeneration of most hepatocytes. B: Kidneys of vaccinated non treated rabbits showing hypertrophied glomerular tuft endothelium and mesingeal cells, hyaline casts in some tubules and cloudy swelling of the tubular epithelium. C: Heart sections of vaccinated non treated group showing moderate congestion of coronary and intermascular blood vessels and capillaries and hyaline degeneration of some muscle fibers. D: Liver of vaccinated group treated with tilmicosin showing normal structures apart of cloudey swelling of some hepatocytes. E: Kidneys of vaccinated rabbits treated with tilmicosin showing hypertrophied glomerular mesingeal cells and cloudy swelling of some renal tubular epithelium. F: Heart of vaccinated animals treated with tilmicosin showing moderate congestion of coronary and intermascular blood vessels and capillaries and hyaline degeneration and vocalization of some muscle fibers).

Discussion

The present study was conducted to evaluate the effects of tilmicosin on rabbit immunity as well as to evaluate its effect on some biochemical parameters and histopathological findings. The results of this study revealed that the vaccinated rabbits when treated S.C with tilmicosin (10 mg/Kg BW/day) for 3 successive days showed no significant changes in the serum urea level, ALT and AST levels compared with the control group. These findings were confirmed by Xie *et al.* [19], Jordan [20], Jordan [21] and Altunok *et al*. [22]. The authors stated that liver function parameters such as ALT, urea and AST were normal, suggesting that the damage of liver was slight and reversible and no tilmicosin treatment-related changes occurred in creatinine. However, Jordan [21] observed that serum ALT after high-dose of tilmicosin in dogs of both sexes was increased by day 12 and continued to increase to the end of the study. This could be attributed to different species under investigation. In the present study, histopathological findings in treated rabbits with tilmicosin showed lesion scores of 1st and 2nd degree (on a scale of 0 to 3) according to Done [23]. These findings were incompatible with Jordan [20] who observed small foci of myocardial necrosis in the papillary muscle as a sign of toxicity. Also, Christodoulopoules [24] reported that lambs injected S.C with tilmicosin 15 mg/kg BW died within 15 minutes.

During necropsy, the heart was found to have multiple ventricular septal defects. Death was attributed to sudden heart failure due to the effects of tilmicosin on the heart. Regarding the effect of tilmicosin on lysozyme activity, this study clearly demonstrated that lysozyme activity increased in the treated-vaccinated group and vaccinated non treated group with maximum levels at 9th day of the experiment. This result was confirmed by Scorneaux and Shryock [25] who reported that tilmicosin enhanced intracellular killing by phagocytes which were detected in studies using swine phagocytes.

Tilmicosin uptake increased the lysosomal enzymes (acid phosphatase, lysozyme and beta-glucuronidas) production. In this study, nitric oxide level in serum was increased in treated and vaccinated groups. This result was in agreement with Cao *et al.* [26] who reported that tilmicosin decreased nitric oxide production. The promotion of B-lymphocytes proliferation in the treated group is compatible with Yun *et al.* [27] who reported that tilmicosin was similar to those of negative control whether *in vitro* or *in vivo*, indicating that this antibiotic did not promote or inhibit lymphocyte proliferation. In our study, tilmicosin stimulated humoral immune response which was inconsistent with Khalifeh *et al.* [28] who reported that tilmicosin reduced the humoral immune response. Also, Guan *et al*. [29] suggested that tilmicosin could suppress the humoral immune response.

Conclusion

Summing up our observations, tilmicosin elicited a significant increase in B-lymphocyte transformation, nitric oxide level and lysozyme activity. Thus indicating its immune stimulation effects with mild reversible impact on liver and kidney functions. The combination of formalinized killed *P. multocida* vaccine and tilmicosin in the prevention and treatment of rabbit pasteurollosis is more effective than using one of them alone.

Conflict of interest

None of the authors have any conflict of interest to declare

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الملخص العربي

الصور المناعية والبيوكيميائية للتلميكوزين في الأرانب

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استهدفت هذه الدراسة تقييم التأثير المناعي للتيلميكوزين (١٠مجم/ كجم) عندما أعطى عن طريق الحقن تحت الجلد للأرانب يومياً ولمدة ثلاثة أيام متتالية حيث تم استخدام عدد ١٥ ذكور الأرانب وتم تقسيمهم الي ٣ مجموعات؛الأولي كضابطة،والثانية محصنة ضد مرض الباستريلا(١مللي) تحت الجلد وغير معالجة،والثالثة محصنة ومعالجة بالتيلميكوزين (١٠ ملجم/كجم وزن لثلاثة أيام متتالية). تم اخذ عينتان من الدم لكل أرنب في الأيام ١ ،٣ ،٩ ،١٤ ،٢١ و٢٨ بعد العلاج لفحص الدم مناعياً وبيوكيميائياً كما تم فحص هستوباثولوجي للكبد والقلب لكل المجموعات. وأظهرت النتائج أن التيلميكوزين يرفع معدلاتالخلايا الليمفاوية ،أوكسيد النيتريك ونشاط الليزوزيم وانزيمات الكبد ووظائف الكلي. وفي الوقت نفسه أدي هذا العلاج إلي عدم وجود تغيرات معنوية في نشاط انزيم الاسبرتيت أمينوترانسفيريز وفي نشاط انزيم الالانين أمينوترانسفيريز ما عدا في اليوم الواحد والعشرين من التجربة الذي شهد انخفاض في نشاط الانزيم. أيضا لم تظهر أي تغيرات معنوية في مستوي الكرياتينين و مستوي اليوريا في المجموعة المحصنة والمعالجة بالتيلميكوزين عند مقارنتها بالمجموعة الضابطة. من خلال فحص التغيرات الهستوباثولوجيه بالقلب والكبد والكلي في المجموعة المحصنة والمعالجه بالتيلميكوزين عند مقارنتهما بالمجموعة الضابطة قدرت شدة الاصابة ب +١ و + ٢. ونستخلص من هذه الدراسة وجود آثار ايجابية للتيلميكوزين علي المناعة وليس له آثار سلبية علي معدلات انزيمات الكبد ووظائف الكلي.