EFFECT OF DIMETHYL DIPHENYL BICARBOXYLATE (DDB) ON SOME IMMUNOLOGICAL AND HISTOPATHOLOGICAL PARAMETERS IN RABBITS VACCINATED WITH PASTEURELLA MULTOCIDA VACCINE

Soliman, A. S.[1]; Shehata, F. E.[1];

El-Dieb, M. K. M.[2] and Helal, A. D.[1]

1- Animal Health Research Institute (Banha Branch)

2- Animal Health Research Institute (Zagazig Branch)

(Biochemistry and Pathology Departments)

ABSTRACT

Twenty apparently healthy Newzealand white male rabbits (average weight = 818.3 + 12.8 grams) were divided into four groups (five animals each), the first group was served as the normal control, the second group was orally administered with 2mg Dimethyl Diphenyl Bicarboxylate (DDB)/kg.b.w. for 28 successive days, the third group was twicely vaccinated (two weeks apart) with pasteurella multocida (sero var 5: A) vaccine, and the fourth group was vaccinated also (as in the third group) along with DDB treatment (as in the second group). At the 29th. day (21 days post second vaccination) the blood, serum, spleen and liver samples were obtained from all animals. The haematological, serological, serum protein electrophoretical, biochemical and histopathological studies were carried out. Results indicated that DDB treotment induced immunostimulant activity due to the significant increase in the total immunoglobulins (Gamma — globulins), lymphocyte percentage and prominent lymphocytic aggregation within the lymphoid follicles of the spleen, but the increase in the indirect Haemagglutination specific antibody titer by DDB treatment was non-significantly against pasteurella multocida vaccine, also the DDB induced significant inerease in red blood corpuscles and haemoglobin concentration and reduced ALT-enzyme activity with the improvement in liver histology in vaccinated rabbits compared to the only vaccinated animals. Based on our study, it should be considered that DDB as a promising immunostimulant, blood tonic and hepatoprotective drug.

INTRODUCTION

The Dimethyl Diphenyl Bicarboxylate (DDB) was chemically named as : Dimethyl-4,4'-dimethoxy-5, 6, 5'-6-dimethylene dioxybiphenyl-1,2'-dicaroxylate **(Akbar et al., 1998)**. Another common name of DDB is : biphenyl Dimethyl Diearboxylate (PMC) wich called also by many authers **(Kim, 2000)**.

DDB is a synthetic derivative compound of Schisandrin C (one principle of Schisandra Chinesis medicinal plant) which now used widely in China as a hepatoproctive drug in human medicine for normalizing liver function with very low side effects **(Li, 1999)**, so that DDB was used for treatment of chronic human hepatitis **(Sinclair, 1998)**.

The hepatoprotective effect of DDB was proven against carbon tetrachloride hepatotoxicity in mice **(Ip et al., 1998)** and against erythromycin hepatotoxicity in rat and goat **(Helal et al., 2003)**, this hepatoprotective effect of DDB (or Schisandrins) may attributed to the stimulation of microsomal metabolizing system P-450, and this may explain their antitoxic, antimutagenic and anticarcinogenic effects **(Li, 1991)** and due also to the stimulation of reduced — glutathione antioxidant system of liver mitochondria **(Ip et al., 1995)**.

The DDB seem to be immunoprotective against the immunosuppresston induced by many immunosuppressive drugs as carbon tetrachloride immunotoxicity in mice **(Ahn and Kim, 1993)**, ketoconazole immunotoxicity in mice **(Kim and Kang, 1999)** and ethanol immunotoxicity in mice **(Kim et al., 2000, & Kim, 2000)**.

DDB could significantly elevated the antiovalbumin IgG in mice by dose level of 6mg/kg.b.w. for 28 days **(Kim et al., 1995)**.

The objective of the present study is to testing and evaluating the immune responses which may be affected by DDB (as a low price, antioxidant, antitoxic and hepatoprotective drug) against pasteurella multocida (haemorrhagic septicemia) vaccine in rabbits, in order to diminuting the pasteurellosis through rising the efficacy of immunization in rabbits, that animal which sharing in animal protein production in Egypt.

MATERIAL & METHODS

Twenty apparently healthy Newzealand white male rabbits (with average body weight of 818.3 ± 12.8 grams) were obtained from private farm in Kaleubia province. All rabbits were put under observation for two weeks, then the rabbits were divided into 4-groups (five animals each). The first group was served as the normal control, the second group was orally administered with 2 mg Dimethyl Diphenyl Bicarboxylate (DDB)/kg.b.w. for 28 suceessive days (the DDB was ob-

tained from Beijing Union pharmaceeutical Factory, Beijing P.R., China), the third group was twicely vaccinated, 2-weeks apart, (at one week before and one week post starting the experiment) with formalized pasteurella multocida (sero var 5 : A) vaccine (kindly obtained from the serum and vaccine research institute, Abbassia, Cairo, Egypt) by dose level of 1c.c./rabbit (subcutaneousely), and the fourth group was vaecinated (as in the third group) along with DDB treatment (as in the second group). All the rabbits of the four groups were weekly weighted in four periods (directly before the experiment and three weeks post starting the experiment). Blood, serum, spleen and liver samples were obtained from all rabbits after sacrificing them at the 29th., day from starting the experiment (21th., day post 2nd., vaccination). The blood samples were used for determination of haemoglobin concentration **(Wintrobe, 1965)**, differential leucocytic count and red blood corpuscle count **(Shalm, 1975)**. The serum samples were used for serological determination of the specific antibody titres against pasteurella multocida (Sero var 5 : A) vaccine, using the indireet (passive) haemagglutination test **(Carter, 1955)**, the serum protein polyacrylamide gel immunoelectrophoresis **(Gordon, 1980)**, total protein **(Doumas et al., 1971)**, total lipids **(Schmit, 1964)**, total bilirubin **(Jendrassiki, 1938)** and the activity of alanine amino transferase (ALT) enzyme activity **(Reitman and Frankel, 1957)**. The spleen and liver tissue samples were fixed in 10% formalin-saline for histopathological technique (Bancroft et al., 1996) and the histopathological lesions were microscopically identified.

The obtained data were statistically analysed using F-test (ANOVA) **(Snedecor and Cochran, 1969)**.

RESULTS

1- The specific antibody titres :

DDB induced non-significant increase of the specific antibody titres against pasteurella multocida vaccine in vaccinated rabbits than that of the vaccinated alone (table, 2).

2- Differential leucocytic count :

a- Neutrophil & Eosinophil percentages : the neutrophil and eosinophil percentages were significantly decreased in the two vaccinated groups of rabbits than the other non-vaccinated groups.

b- Lymphocyte percentage : the lymphocyte percentage increased significantly in rabbits treated with DDB, than control group, but in the vaccinated rabbits, DDB induced non-significant increase of lymphocyte percentage than vaccinated non-treated animals.

c- Monocyte and Basophil percentages : the monocyte and basophil percentages were non

significantly changed within the groups (table, 3).

3- Serum protein immunoelectrophoresis :

a- Alpha (a) globulin fractions : DDB treatment of non-vaccinated rabbits induced significant increase of a-globulins than the control rabbits.

b- Beta (b) globulins : the b-globulins non-signifieantly changed within groups of the rabbits.

c- Gamma (g) globulins (immunoglobulins): the g-globulins were signifieantly increased in both DDB treated groups of rabbits (vaccinated or non-vaccinated) than the other corresponding non-DDB treated groups.

d- Total globulins : The total globulins were increased significantly in all groups than control.

e- Albumin : the albumin was significantly increased by the two vaccinated groups of rabbits than control rabbits. DDB not affect the albumin concentration. The different protein fractions are tabulated in table (4).

4- Some serum biochemical constitutents :

a- Alanine amino transferase (ALT) enzyme activity : the ALT enzyme level was reduced in DDB treated groups than the other groups (table, 5).

h- Total bilirubin and total protein : Both the total bilirubin and the total protein were significantly increased in both vaccinated groups than that of the two other non-vaccinated groups (table, 5).

5- The red blood corpuscle (RBCs) count : the RBCs was significantly increased by DDB treated groups of rabbits than that of the other groups (table, 6).

6- The haemoglobin (Hb) concentration : the Hb concentration only increased significantly by DDB treated (non-vaccinated) rabbits than control (table, 6).

7- The body weights (B.W.): The B.W. was non significantly affected between the four groups of rabbits in the four studied periods (table, 7).

8- The histopathologieal lesions : the microscopical examination of the spleen and liver tissues of rabbits were recorded in the following table (1):

DISCUSSION

No available data concerning the use of DDB as a direct immunostimulant drug, especially

against certain vaccination or disease, but many authers were used this drug as a protective agent against the immunosupression induced by the immunodepressants for several years ago.

In the present study, the DDB treatment seem to be immunostimulant due to its induction of significant increase of both immunoglobulins (gamma-globulins) and the circulating lymphocytes than the control rabbits, but the specific antibody titer of the passive haemagglutination (H.A.) test against pasteurella multocida vaccine increased non-significantly by the DDB treatment than that of the vaccinated alone. This non-significant increase of H.A. titer perhaps attributed to the small dose of DDB used (2mg/kg.b.w., a dose near that used for human therapy) compared to the dose level of 6mg/kg.b.w. which could induced a significant increase of the specific H.A. titre againt sheep RBCs immunization in carbon tetrachloride intoxicated mice **(Ahn and Kim, 1993)**. So that, different levels above 2mg/kg.(with safety evaluation) should be tried to increase the H.A. titre against rabbit pasteurellosis along with determining the type of immunoglobulin(Ig) associated through further investigations.

The immunoglobulins (g-globulins) in animals were : IgG, IgM, IgA, and IgE (IgD in man only) **(Mancini et al., 1965 & Iamarino, 1972)**, while albumin, α-and β-globulins are synthesized in the liver, the g-globulins are synthesized by the plasma cells which maturated from the B-lymphocytes in the spleen, bone marrow and lymph nodes **(McPherson, 1984 & Duncan and Prass, 1986)**. So that the hypergamma γ- globulinemia induced by DDB treatment in the present study may explain the significant increase of the circulating lymphocytes, the prominent increase of lymphocytic aggregation in the lymphoid follicles of the spleen and the perivascular aggregation of lymphocytes in the liver of DDB treated and vaccinated group than that of vaccinated alone. Approximately 20% of the circulating lymphocytes are B-lymphocytes and the remainder being the T-lymphocytes **(Jain, 1960)**.

The current study revealed hyper alpha (α) globulinemia in DDB treated (non-vaccinated) rabbits than control animals. The elevated levels of some α-globulins have been reported in rats with some chemicals as the 3-methyl -4- dimethyl aminobenzene administration **(Dolezalova et al., 1983)**.

The present study revealed the presence of significant decrease of either neutrophils (neutropenia) or eosinophils (eosinopenia) in the two vaccinated groups than control. Neutropenia may occur following diphenyl hydantoin administration **(Young et al., 1975)**.

Our study revealed a significant decrease of ALT enzyme activity in DDB treated rabbits than non-treated ones. Such results could be obtained in rat and goat by **Helal et al. (2003)** and this may be attributed to the antioxidant and antitoxic effect of DDB **(Li, 1991)** and consequently DDB suggested to protect hepatocytes from fast rate of degeneration which may occur through

the normal degeneration and regeneration process of hepatocytes, and this need further clarification.

The present study revealed a significant increase of red blood corpuscles (RBCs) count in the DDB treated groups than the other non-treated groups, but the haemoglobin (Hb) concentration increased significantly only by DDB treated (non-vaccinated) group than control. This increase of RBCs and Hb suggesting the haematonic effect of DDB therapy in rabbits, perhaps due to the protective effect of DDB against RBCs haemolysis and consequently lead to prolonging the RBCs life span in a manner similar to hepatoprtective effect of DDB through its antioxidant and antitoxic properties **(Ip et al., 1998)**.

Based on the current study, it could be concluded that DDB showed a promising immunostimulant effect (due to the significant increase of either total immunoglobulins or lymphocyte percentage), blood tonic effect (due to the significant inercase of either RBCs count and Hg. concentration) and hepatoprotective effect (due to lowering ALT-enzyme activity). The other various immune responses at various levels of DDB (with safety evaluation) should be tried to evaluate the use of DDB as an immunostimulant drug to various vaccines or infectious diseases, beside the using it either as an immunoprotective agent against the immunodepressants or as a hepatoprotective agent against the hepatotoxicants.

Table (1): The histopathological lesions of DDB treated rabbits for 28 days (vaccinated and non-vaccinated with pasteurella (multocida vaccine).

Groups	Spleen	Liver
DDB treated (non-vaccinated) group (2mg/kg.b.w.) for 28 days	* Slight lymphocytic aggregation in the lymphoid follicles than control.	* Slight degenerative changes.
Vaccinated group	* Slight to moderate aggregation of lympho-cytes in the lymphoid follicles. * Depletion of the white pulps (Fig.1).	* Dilatation of the central veins. * Clear vacuolation of the hepatocytes. * Degenerative changes of the hepatocytes (Fig.3)
Vaccinated + DDB treated group	* Prominent increase of lympho-cytic aggregations in the lymphoid follicles. * Mild hyperplasia in the white pulps. * Hyalinized central arterioles. * Slight hemosiderosis (Fig.2)	* Slight congestion of the central veins. * Mild to Prominent perivascular lymphocytic aggregations. * Slight degenerative changes of hepatocytes * Mild leucocytic aggre-gation in the liver tissue (Fig.4).

Table (2): The specific antibody titers of the rabbits treated with DDB (2mg/kg.b.w. for 28 days) and/or vaccinated with pasteurella mulltocida (Sero var 5 : A) vaccine as measured with the indirect (passive) haemagglutination test.

Groups	Control group	DDB treated group	Vaccinated group	Vaccinated + DDB treated group	LSD (at $P \leq 0.05$)
Titer ranges	1/2 – 1/8	1/2 – 1/8	1/512 – 1/2048	1/512- 1/4096	--
Log_{10}-values of the reciprocal titers (Means ± SE)	0.602^a ± 0.085	0.602^a ± 0.120	2.860^b ± 0.135	3.161^b ± 0.135	0.440

N.B. : 1- LSD = Least Significant Difference (at $P \leq 0.05$).
2- Different littes in rows denote significant change (at $P \leq 0.05$)

Table (3): The differential leucocytic count of rabbits treated with DDB (2mg/kg.b.w. for 28 days) and/or vaccinated with pasteurella multocida vaccine.

Groups	Neutrophil (%)	Lymphocyte (%)	Monocyte (%)	Eosinophil (%)	Basophil (%)
Control group	$23.756^{a} \pm 3.33$	$58.58^{a} \pm 3.71$	$7.974^{a} \pm 0.69$	$7.758^{a} \pm 1.40$	$1.93^{a} \pm 0.23$
DDB treated group (2mg/kg.b.w. for 28 days)	$17.42^{a} \pm 2.02$	$70.67^{b} \pm 2.35$	$6.81^{a} \pm 0.539$	$3.538^{b} \pm 0.72$	$1.56^{a} \pm 0.62$
Vaccinated group	$11.29^{b} \pm 2.83$	$81.402^{c} \pm 8.57$	$4.33^{a} \pm 0.86$	$2.182^{b} \pm 0.312$	$0.80^{a} \pm 0.24$
Vaccinated + DDB treated group	$6.548^{b} \pm 0.75$	$83.30^{c} \pm 1.74$	$6.68^{a} \pm 1.32$	$1.822^{b} \pm 0.44$	$1.662^{a} \pm 0.46$
LSD (at $P \leq 0.05$)	9.446	10.441	N.S.	2.922	N.S.

N.B. :

1- Different litters in columns denote significant change between means (at $P \leq 0.05$).

2- N.S. = Non-significant change.

3- LSD = Least Significant Different (at $P \leq 0.05$)

Table (4): The serum protein immunoelectrophoresis of rabbits treated with DDB (2mg/kg.b.w. for 28 days) and/or vaccinated with pasteurella multocida vaccine.

Groups	Alpha(α) globulins (g/dl)	Betal (β) Globulins (g/dl)	Gamma (γ) Globulins (g/dl)	Total globulins (g/dl)	Albumin (g/dl)	Total protein (g/dl)
Control group	1.047[a] ± 0.165	1.210[a] ± 0.084	0.607[a] ± 0.111	2.864[a] ± 0.335	3.403[a] ± 0.316	6.267[a] ± 0.115
DDB group (2mg/kg.b.w. for 28 days)	1.770[b] ± 0.97	1.260[a] ± 0.258	1.705[b] ± 0.134	4.735[b] ± 0.319	3.195[a] ± 0.306	7.93[b] ± 0.298
Vaccinated group	1.186[a] ± 0.291	1.612[a] ± 0.111	0.693[a] ± 0.098	3.491[c] ± 0.311	4.363[b] ± 0.393	7.854[b] ± 0.122
Vaccinated + DDB treated group	1.270[a] ± 0.226	1.271[a] ± 0.364	1.176[c] ± 0.102	3.717[d] ± 0.226	4.290[b] ± 0.253	8.007[b] ± 0.298
LSD (at $P \leq 0.05$)	0.298	N.S	0.356	0.181	0.397	0.674

N.B. : 1- LSD = Least Significant Difference (at $P \leq 0.05$).
2- Different litters in columns denote significant change (at $P \leq 0.05$)

Table (5): Some serum biochemical constituents of rabbits treated with DDB (2mg/kg.b.w. for 28 days) and/or vaccinated with pasteurella multocida vaccine.

Groups	ALT-enzyme activity (U/L)	Total Bilirubin (mg/dl)	Total Protein (g/dl)
Control Group	12.096[a] ± 1.843	0.286[a] ± 0.032	6.267[a] ± 0.115
DDB group (2mg/kg.b.w. for 28 days)	4.752[b] ± 0.058	0.349[a] ± 0.003	7.930[b] ± 0.298
Vaccinated group	9.504[a] ± 1.958	0.637[b] ± 0.048	7.854[b] ± 0.122
Vaccinated + DDB treated group	3.832[b] ± 0.266	0.762[b] ± 0.045	8.007[b] ± 0.298
LSD (at $P \leq 0.05$)	3.607	0.134	0.674

N.B. : 1-LSD = Least Significant Difference (at $P \leq 0.05$).
2- Different litters in columns denote significant change (at $P \leq 0.05$)

Table (6): The Red Blood Corpuscles (RBCs) count and the Haemoglobin concentration of the blood of DDB treated (vaccinated and non-vaccinated) rabbits.

Groups	Control group	DDB/ treated group (2mg/kg.b.w. for 28 days)	Vaccinated group	Vaccinated + DDB treated group	LSD (at $P \leq 0.05$)
RBCs count (million/cu.m.	3, 540,000[a] ± 141,421	6,450,000[b] ± 126,492	3,690,000[a] ± 89,443	5,320,000[c] ± 219,818	273,028
Haemoglobin conc. (g/dl.)	19.855[a] ± 1.030	24.765[b] ± 0.346	19.590[a] ± 0.980	20.39[a] ± 0.700	3.091

N.B.:
- The different litters in rows denotes significant changes between means (at $P \leq 0.05$)
- LSD = Least Significant Difference (at $P \leq 0.05$).

Table (7): The body weights (B.W.) of the different groups of rabbits treated with DDB and /or vaccinated with pasteurella multocida vaccine.

Groups	Before experiment (gm)	After 1 week (gm)	After 2 weeks (gm)	After 3 weeks (gm)
Control group	822.8[a] ± 32.669	871.1[a] ± 36.415	990.5[a] ± 28.69	1132.2[a] ± 24.74
DDB group (2mg/kg.b.w. for 28 days)	836.4[a] ± 37.57	895.1[a] ± 35.12	1042.2[a] ± 28.16	1125.1[a] ± 17.23
Vaccinated group	755.2[a] ± 58.77	915.1[a] ± 63.83	1054.5[a] ± 88.17	1035.4[a] ± 63.99
Vaccinated + DDB treated group	838.8[a] ± 47.02	862.5[a] ± 56.25	940.9[a] ± 79.80	1051[a] ± 97.8
LSD (at $P \leq 0.05$)	N.S.	N.S.	N.S.	N.S.

N.B. ; N.S. = non-significantly changed

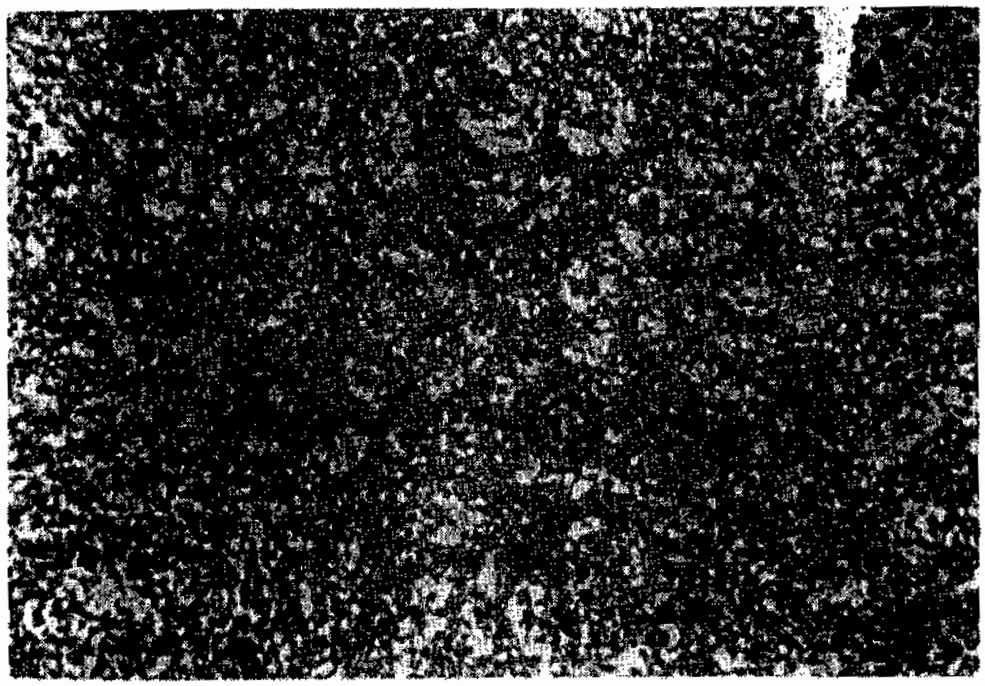

Fig. (1) : Spleen section of rabbit vaccinated with pasteurella multocida vaccine, Showing depleted white pulps (H & E X 150).

Fig. (2) : Spleen section of rabbit orally administered with 2mg DDB/kg.b.w. for 28 days and vaccinated with pasteurella multocida vaccine, showing mild hyperplasia in the white pulps and hyalinized central arterioles (H & E X 100)

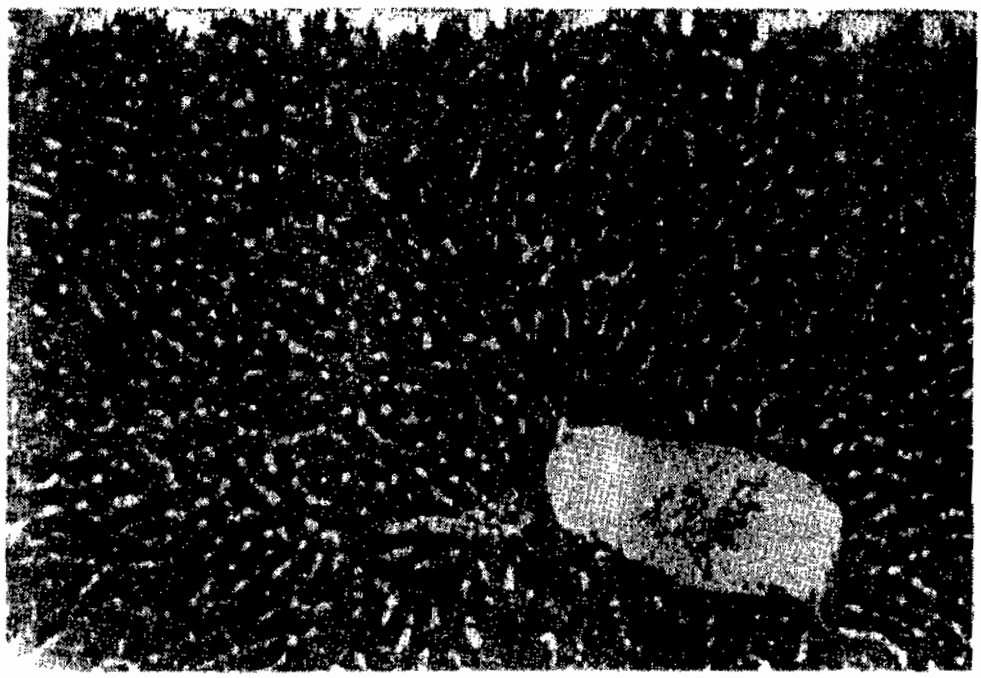

Fig. (3) : Liver section of rabbit post pasteurella multocida vaccination showing vacuolation of the hepatocytes, (H & E. x150)

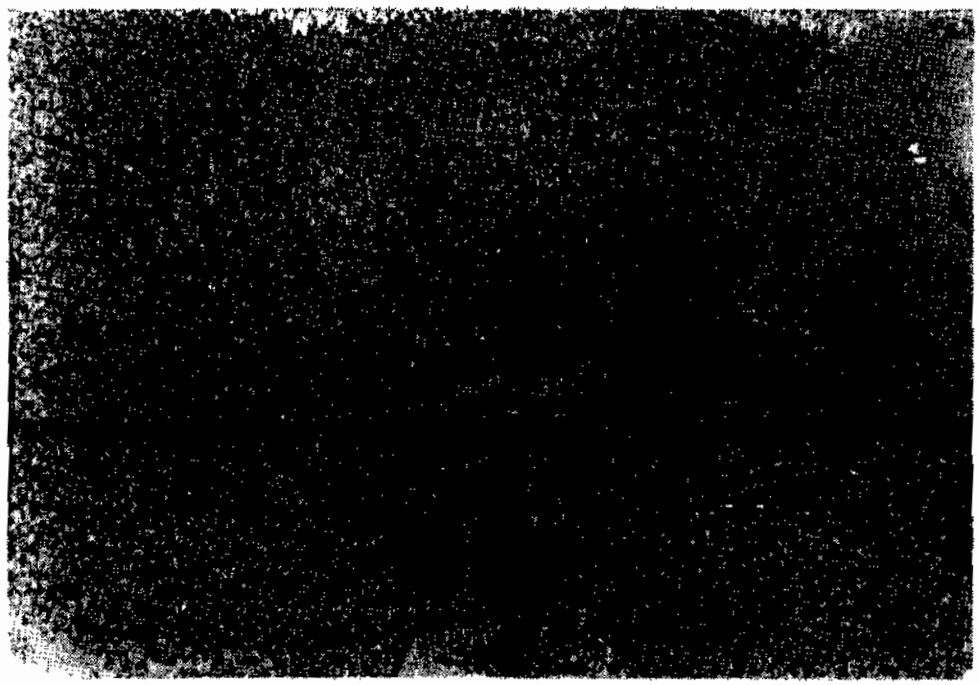

Fig. 4) : iver section of rabbit administered 2mg DDB/kg.b.w. for 28 days and vaccinated with pasteurella multocida vaccine, showing mild leucocytic aggregation in the liver tissue (H, E. X 100)

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الملخص العربى

تأثير الداى ميثيل داى فنيل باى كربوكسيلات (DDB) على بعض المعالم المناعية والهستوباثولوچية فى الأرانب المحصنة بلقاح الباستيريللا ملتوسيدا

المشتركون فى البحث

عبدالحفيظ السيد سليمان، د/ فوزى إبراهيم شحاته

د/ محمود كمال مصطفى الديب، د/ علاء الدين هلال على

١- معهد بحوث صحة الحيوان الفرعى بمنها

٢- معهد بحوث صحة الحيوان الفرعى بالزقازيق

تم تقسيم عدد من ذكور الأرانب النيوزيلاندى البيضاء السليمة (متوسط الوزن ٣ر٨١٨ + ٨ر١٢ جرام) إلى أربعة مجموعات (٥ أرانب بالمجموعة)، واعتبرت المجموعة الأولى كضابط للتجربة، والمجموعة الثانية أعطيت مركب الداى ميثيل داى فنيل باى كربوكسيلات (DDB) (الحبة الصفراء) / كجم وزن بالفم لمدة ٢٨ يوم متتالية، وحصنت المجموعة الثالثة بلقاح الباستيريللا ملتوسيدا (سيرو فار ٥ : أ) مرتين (بينهما ١٤ يوم)، أما المجموعة الرابعة فقد عولجت بـ ألـ (بنفس الطريقة فى المجموعة الثانية) وحصنت أيضاً (بنفس الطريقة فى المجموعة الثالثة)، وتم أخذ عينات دمDDB وسيرم وطحال وكبد من حيوانات المجموعات الأربع وذلك فى اليوم التاسع والعشرون (اليوم ١ بعد التحصين الثانى وذلك لعمل الاختبارات الهيماتولوچية والسيرولوچية والبيوكيميائية والفصل الكهربى لبروتين مصل الدم، وتم أيضاً وزن جميع الأرانب فى أربع فترات إسبوعياً.

وقد أوضحت النتائج أن العلاج بعقار الـ DDB قد نتج عنه نشاطاً منبهاً لجهاز المناعة وذلك نتيجة الزيادة المعنوية للجلوبيولينات المناعية ونسبة الخلايا الليمفاوية بالدم ووجود تجمع ظاهر للخلايا الليمفاوية بالحويصلات الليمفاوية بالطحال، ولكن الزيادة فى مستوى الأجسام المناعية الخاصة المضادة للقاح الباستيريللا ملتوسيدا كانت زيادة غير معنوية، وكذلك أحدث العلاج بمركب الـ زيادة معنوية فى كل من خلايا الدم الحمراء وتركيز هيموجلوبين الدم ونقص معنوى فى مستوى إنزيم الألانين أمينو ترانس فيريز (ALT)، وتحسن فى الشكل التركيبى لخلايا وأنسجة الكبد فى الحيوانات المحصنة والمعالجة بالعقار عن المحصنة فقط.

ومن خلال هذه الدراسة فقد أمكن إستنتاج أن لعقار الـ DDB تأثير واعد منبه للمناعة وكمقوى الدم وكواقى للكبد.