犬糸状虫ミクロフィラリア陽性犬のミルベマイシンD投与に伴う有害反応の抑制

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Prevention of Adverse Reactions following Milbemycin D administration to Microfilaremic Dogs Infected with *Dilofilaria immitis*

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ABSTRACT. Some adverse reactions such as shock-like reaction and dirofilarial hemoglobinuria (caval syndrome) occasionally occurred in microfilaremic dogs following milbemycin D (Milbe) administration. This study was carried out to seek the prevention of these adverse reactions. In two groups containing 16 and 9 dogs respectively which were administered either chlorpheniramine maleate (1 mg/kg) or indomethacin (2.5 mg/kg) simultaneously with Milbe (1 mg/kg), the incidence of clinical signs such as the pale color of the visible mucous membranes, respiratory disorders, caval syndrome and shock-like reaction as well as changes in clinical parameters such as RBC and WBC counts, WBC profile and serum total protein, were almost equal to that observed in the group administered Milbe alone. In 41 dogs administered prednisolone (1 mg/kg) simulaneously with Milbe (1 mg/kg), no shock-like reaction was observed. Changes in clinical parameters were different from those in the group administered Milbe alone, whereas some clinical signs of adverse reactions, including caval syndrome, were observed. These results indicated that prednisolone was effective for prevention of the shock-like reaction in microfilaremic dogs induced by Milbe.—KEY WORDS: adverse reaction, dog, heartworm disease, milbemycin D, prophylaxis.

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Milbemycin D (Milbe) is a clinically safe drug for dogs without microfilaremiae of *Dirofilaria immitis* (heartworm) at a prophylactic dose (1 mg/kg), but occasionally induces some adverse reactions including dirofilarial hemoglobinuria (caval syndrome) and shock-like reaction in microfilaremic dogs [10, 12, 13]. The mechanism of these adverse reactions has not been clarified yet, but it is suspected that some immunological reactions against the substances released from microfilariae (mf) affected by Milbe are involved, as the reaction by diethylcarbamazine (DEC) [7, 9]. This study was carried out to examine whether these adverse reactions can be prevented by immunosupressive and/or anti-inflammatoric drugs.

MATERIALS AND METHODS

A total of 76 dogs of both sexes, various breeds and ages were used in this study. All of them were naturally infected with heartworms, and microfilariae (mf) of *Dirofilaria immitis* were detected in the peripheral blood. Milbe was administered orally to each dog at a dose of 1 mg/kg. Prednisolone was administered intramuscularly or orally to 41 dogs at a dose of 1 mg/kg simultaneously with Milbe (PD-Milbe group). Prednisolone alone was administered orally to 10 dogs at a dose of 1 mg/kg, in order to examine effects of this drug when administered alone (PD group). Chlorpheniramine maleate, which is an antihistaminic, was administered orally to 16 dogs at a dose of 1 mg/kg simultaneously with Milbe (CP-Milbe group). Indomethacin was administered

Table 1. Clinical findings after drug administration in each group

Sign	Group			
	PD-Milbe (n=41)	PD (n=10)	CP-Milbe (n=16)	IM-Milbe (n=9)
Pale color in visible mucous membranes	6 (15%)	0	5 (31%)[a]	1 (11%)
Respiratory disorder[b]	3 (7%)	0	1 (6%)	2 (22%)
Arrythmia	2 (5)	0	1 (6)	1 (11)
Dullness of heart sound	0	0	0	1 (11)
Accentuated second heart sound	0[a]	0	1 (6)	0
Caval syndrome	4 (10)	0	3 (19)	1 (11)
Shock-like reaction	0[a]	0	1 (6)	1 (11)

a) Significantly different from the mf-positive group ($p<0.05$).
b) Slight dyspnea and/or rough vesicular breath.

orally to 9 dogs at a dose of 2.5 mg/kg simultaneously with Milbe (IM-Milbe group).

All the dogs underwent clinical examinations and blood sampling for laboratory tests before and at 3, 6 and 24 hr after drug administration. The methods of clinical examination and laboratory tests were the same as in the previous report [12]. These data were analyzed for statistical significance applying Fisher exact probability to clinical signs of adverse reactions and paired *t*-test to the data obtained by the laboratory tests.

RESULTS

The incidence of clinical signs of adverse reactions after drug administration is shown in Table 1. In the PD-Milbe group, 5 to 15% of dogs showed pale color of the visible mucous membranes, respiratory disorders (slight dyspnea and/or rough vesicular breath), arrhythmia and caval syndrome, but not observable dullness of heart sound, accentuated second heart sound or shock-like reaction. In the PD group, no clinical signs of adverse reactions were observed. In the CP-Milbe and IM-Milbe groups, 6 to 31% dogs showed pale color of the mucous membranes, respiratory disorders, arrhythmia, dullness of heart sound, accentuated second heart sound, caval syndrome and shock-like reaction.

Clinical data in each group, excluding those of dogs with shock-like reaction and caval syndrome, are shown in Tables 2 and 3. In the PD-Milbe group, body temperature, RBC count, serum total protein (T.P) concentration and mf count decreased, and total WBC and neutrophil counts and A/G ratio increased at 3, 6 or 24 hr after drug administration. As to the relationship between T.P concentration and A/G ratio, concentrations of both albumin and globulin decreased, but the decrease of the latter was larger than that of the former. In the PD group, body temperature, heart rate, and RBC, eosinophil and lymphocyte counts decreased at 3 and/or 6 hr after drug administration, and total WBC and lymphocyte counts and T.P concentration increased at 24 hr. In the CP-Milbe and IM-Milbe groups, body temperature, counts of total WBC, neutrophil and eosinophil, T.P concentration and mf counts decreased follow-

Table 2. Clinical data in the PD-Milbe and PD groups

Item	PD-Milbe group (n=37)				PD group (n=10)			
	Pre-administration	Post-administration			Pre-administration	Post-administration		
		3 hr	6 hr	24 hr		3 hr	6 hr	24 hr
Body temperature (°C)	38.9±0.4[a]	38.7±0.3[b]	38.7±0.4[b]	39.0±0.5	39.0±0.4	38.7±0.3[b]	38.6±0.3[b]	38.8±0.4[b]
Heart rate (beat/min)	117±20	114±22	114±23	119±27	123±20	118±21[b]	110±19[b]	118±25
Systolic blood pressure (mmHg)	137±16	128±19	135±17	133±14	137±10	136±13	134±12	139±13
RBC ($\times 10^4/\mu l$)	628±96	605±99[b]	596±104[b]	585±94[b]	565±57	548±54[b]	551±42	561±41
WBC($\times 10^2/\mu l$)	147±47	152±48[b]	191±53[b]	129±44[b]	146±74	208±82[b]	252±82[b]	148±93
Neutrophil ($\times 10^2/\mu l$)	102±46	131±44[b]	177±52[b]	102±38	98±43	178±68[b]	232±75[b]	84±42
Eosinophil ($\times 10^2/\mu l$)	12±7	3±3[b]	1±1[b]	4±5[b]	22±22	9±12[b]	3±4[b]	16±22
Lymphocyte ($\times 10^2/\mu l$)	31±18	17±9[b]	11±8[b]	23±17[b]	28±16	20±12	16±10[b]	37±23[b]
Serum total protein (g/dl)	6.59±0.68	6.22±0.73[b]	6.41±0.71[b]	6.54±0.74	6.32±0.63	6.3±0.62	6.4±0.49	6.63±0.63[b]
A/G ratio	0.86±0.29	0.90±0.27[b]	0.90±0.28[b]	0.85±0.29	0.91±0.23	0.92±0.26	0.97±0.28	0.91±0.23
GPT (IU/l)	51.9±35.5	ND[c]	ND	63.0±31.4	50.6±19.5	ND	ND	46.8±20.6
Microfilaria (/200 μl)	5041±6753	1351±1327[b]	802±862[b]	539±724[b]	6627±6810	4743±4735[b]	5333±3587	6339±6061

a) Mean ± standard deviation. b) Significantly different from pre-administration level ($p<0.05$). c) Not done.

ing drug administration. The RBC count increased in some dogs while decreased in others. The mf counts at 24 hr after drug administration in each group except the PD group generally decreased by 4 to 16% compared to those before drug administration.

DISCUSSION

Shock-like reaction and caval syndrome are clinically important adverse reactions observed after Milbe administration. Pale color of the visible mucous membranes and respiratory disorders have not been recognized as serious clinical problems, because they are slight and temporary. It is considered that chlorpheniramine maleate and indomethacin seldom serve to prevent adverse reactions occurring after Milbe administration in microfiraremic dogs, based on the result that the incidence of the adverse reactions and changes in clinical data were quite similar to those in the group administered Milbe alone [12]. On the other hand, prednisolone prevented the development of shock-like reaction, and clinical data such as body temperature, RBC and WBC counts, WBC profile and A/G ratio were different from those in the group administered Milbe alone. The incidence of shock-like reaction was 11%, body temperature and RBC counts varied with individual dogs, WBC counts decreased following decrease of neutrophils, T.P concentration decreased and no changes in A/G ratio in the group administered Milbe alone [12]. These results agreed with those of previous

Table 3. Clinical data in the CP-Milbe and IM-Milbe groups

Item	CP-Milbe group (n=12)				IM-Milbe group (n=7)			
	Pre-administration	Post-administration			Pre-administration	Post-administration		
		3 hr	6 hr	24 hr		3 hr	6 hr	24 hr
Body temperature (°C)	38.9±0.4[a)]	39.0±0.5	39.0±0.5	39.0±0.5	38.8±0.4	38.5±0.5[b)]	38.6±0.4	38.9±0.6
Heart rate (beat/min)	110±21	109±26	119±24	117±22	120±22	119±32	139±31	125±16
Systolic blood pressure (mmHg)	123±13	113±18	122±14	123±11	142±13	129±30	144±13	135±15
RBC ($\times 10^4/\mu l$)	562±138	581±155	579±152	554±136	635±119	635±143	661±175	605±109
WBC ($\times 10^2/\mu l$)	134±45	95±29[b)]	121±23	118±36	170±29	122±30[b)]	126±24[b)]	120±22[b)]
Neutrophil ($\times 10^2/\mu l$)	98±41	78±26[b)]	106±22	88±34	112±29	85±39[b)]	93±23	78±28[b)]
Eosinophil ($\times 10^2/\mu l$)	14±9	3±2[b)]	4±4	11±5	20±11	5±5[b)]	8±10[b)]	14±11
Lymphocyte ($\times 10^2/\mu l$)	21±11	13±7[b)]	11±5	18±10	36±20	31±21	24±15	27±19
Serum total protein (g/dl)	5.85±0.76	5.43±0.69[b)]	5.53±0.65[b)]	5.80±0.59	6.83±0.76	6.49±0.74[b)]	6.30±0.70[b)]	6.56±0.37
A/G ratio	1.01±0.2	1.0±0.26	1.0±0.29	0.9±0.23	1.03±0.25	1.05±0.30	1.04±0.27	0.95±0.21
GPT (IU/l)	53±31	ND[c)]	ND	89±80[b)]	36.4±3.5	ND	ND	57.5±75.9
Microfilaria (/200 μl)	3805±3541	494±524[b)]	270±312[b)]	153±210[b)]	1799±3082	1210±1636	612±890[b)]	293±562

a) Mean ± standard deviation. b) Significantly different from pre-administration level (p=0.05). c) Not done.

studies, reporting that shock-like reactions after DEC administration in human with onchocerciasis were prevented by glucocorticoids, but not by antihistaminics and indomethacin [1, 2, 3]. This fact might suggest that immunological reactions were not directly involved in the Milbe reactions as reported by Boreham [3] on the DEC reaction.

Glucocorticoids improve hemodynamics, inducing elevation of blood pressure, increase of cardiac output and decrease of total peripheral resistance, and it has been considered that these reactions might serve to prevent or ameliorate rather than cause anti-inflammatory and immuno-suppressive effects in hemorrhagic, endotoxic and cardiologic shocks [4, 5, 6, 8, 11, 14, 15]. Although the precise mechanism is unknown, it is suspected that the action of prednisolone on hemodynamics plays an important role in the prevention of shock-like reaction after Milbe administration.

Caval syndrome could not be prevented by prednisolone. However, it has not posed much clinical problems, because caval syndrome, which occurs within several hours after Milbe administration, can be easily treated by surgical removal of heartworms in the early stage [10]. It has been considered that caval syndrome is caused by the movement of heartworms from the pulmonary arteries to the tricuspid valve orifice following the suppression of cardiac function after Milbe administration [10]. These findings suggest that prednisolone prevents the development of severe circulatory disturbances such as the shock-like reaction,

however, not all the slight disturbances, and caval syndrome can be induced in some dogs.

From the above results, it is considered that Milbe could be safely applied to microfilaremic dogs, provided that a glucocortiocoid is administered simultaneously with Milbe or before Milbe administration as reported on the hemorrhagic shock [14]. The administration of glucocorticoids is needed only at the first administration of Milbe, because the shock-like reaction does not occur after the second administration [13].

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要　　約

犬糸状虫ミクロフィラリア陽性犬のミルベマイシンD投与に伴う有害反応の抑制：佐々木栄英・北川均・石原勝也・柴田昌利（岐阜大学農学部）——ミクロフィラリア（mf）陽性犬では1 mg/kgのmilbemycin D（Milbe）の投与で有害反応が発生する場合がある．この反応を抑制する目的で，mf陽性犬41頭にprednisolone（PD，1 mg/kg），16頭にchlorophenilamine maleate（CM，1 mg/kg），9頭にindomethacin（ID，2.5mg/kg）をそれぞれMilbe（1 mg/kg）と同時に投与し，臨床観察をした．その結果，CMまたはIMの併用群では有害反応の抑制効果は認められなかった．しかし，PDの併用群ではcaval syndromeなどの散発を認めたが，ショック様反応は発生しなかった．以上の結果からpredonisoloneの併用はMilbe投薬によるショック様反応の抑制効果があると思われる．