犬糸状虫予防薬ミルベマイシンDの臨床応用

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Clinical Application of Milbemycin D as a Prophylactic Agent against *Dirofilaria immitis* Infection in Dogs: Clinical Findings in Dogs with Shock-like Reaction

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ABSTRACT. A shock-like reaction occurred in 20 (8%) of 243 *Dirofilaria immitis*-uninfected and infected dogs, after milbemycin D administration at a dose of 0.1–5 mg/kg. All dogs with the reaction were infected, and microfilariae (mf) were detected in peripheral blood (19 dogs) or by histopathological examination (1 dog). The number of circulating mf before administration and their decrease rate after treatment were not related to the occurrence and intensity of the shock-like reaction. The reaction occurred 1.5 to 4 hr after administration, and recovery took place 1 to 4 hr after the onset of the reaction without any treatment in all dogs. Clinical signs of the affected dogs were depression, paleness and/or slight cyanosis of the mucous membranes, weak pulse, coldness of skin, dyspnea, staggering, prostration, tendency to heart rate decrease and remarkable decrease of blood pressure. Disappearance or relief of arrhythmia, increased height (mV) of the R wave, sagging of the ST segment and inversion of the T wave were seen on electrocardiogram. On the hematological findings, total WBC and neutrophil counts decreased at the early stage of the reaction and increased at the latter stage, and RBC, eosinophil counts and serum total protein concentration decreased at the reaction. Serum glucose concentraion temporarily increased at the reaction. Serum enzyme activities considerably increased and mf count remarkably decreased at 24 hr after administration. The dogs which showed the shock-like reaction at the first administration did not display any such reaction at the second or third administrations.—KEY WORDS: adverse reaction, canine heartworm, milbemycin D, shock-like reaction.

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In the previous report [16], the authors reported that milbemycin D (Milbe) was a clinically safe drug when administered to *Dirofilaria immitis* (heartworm)-uninfected or microfilariae (mf) negative dogs in a recommended dose as a prophylactic for heartworm infection, but induced some adverse reaction in mf positive dogs. The shock-like reaction was the most severe finding among the adverse reactions. It has been well known that diethylcarbamazine (DEC) induced a shock-like reaction in human [3, 8, 10] and dogs [1, 2, 7, 13–15] with filariasis, and it was considered that these reactions were involved by immunological reaction with destroying mf [3, 5–7, 9, 14, 15, 17, 18]. However, it has not been reported that other microfilaricides such as dithiazanine iodide and levamisole induced a shock-like reaction. Recently, it was reported that avermectin also induced shock-like reaction in mf positive dogs after treatment [11]. This drug [4] has a chemical structure similar to that of Milbe [19] and killed mf [11], but the reaction by avermectin has been little studied. The present study described clinical findings in dogs with shock-like reaction by Milbe, and compared with the reaction by DEC to find some clues to solve the mechanism of shock-like reaction by Milbe.

MATERIALS AND METHODS

Twenty dogs were used in this study, in which a shock-like reaction was induced in

clinical tests with Milbe conducted from November, 1983 to October, 1985. A total of 243 dogs, uninfected (61), circulating mf negative (55) and circulating mf positive (127) dogs were used for the clinical tests (Table 1). The dogs displaying the reaction were mongrels of both sexes, 1 to 10 years old of presumed age, 5 to 15 kg in body weight. Milbe (Sankyo Co., Ltd. Tokyo) was used as a powder preparation containing 1%.

Each dog was orally given a dose of 0.1 to 5 mg/kg of Milbe in gelatin capsules. Their behavior and clinical signs were carefully observed at 30 or 60 min interval until 6 hr post-administration. The clinical data and blood samples were obtained at pre-administration, at detection of the shock-like reaction (at the reaction), and at 6 and 24 hr post-administration.

To determine whether the shock-like reaction recurred, Milbe was repeatedly administered to the dogs evidencing the shock-like reaction at the first administration. The second administration of Milbe (second trial) was made 9 to 53 days after the first administration in 7 dogs, and the third trial was made 96 to 194 days after the second trial in 4 dogs.

Clinical examinations were made with the same methods used in previous studies [12, 16].

RESULTS

The incidence of the shock-like reaction was 8% (20/243 dogs) in all dogs, but 15% (19/127 dogs) in mf positive dogs (Table 1). There was no difference in incidence between the dose of 1 and 5 mg/kg. The incidence from doses of 0.1 or 0.2 mg/kg appeared to be higher than that from 1 or 5 mg/kg, but this difference was not significant, because only a small number of dogs were examined in former doses. The shock-like reaction developed at 1.5 to 4 hr post administration. The onset time of the reaction tended to delay, and clinical signs were slight in a small dose.

There are mild (5 dogs), moderate (3 dogs) and severe (12 dogs) cases in the intensity of the reaction. The mild cases showed sudden depression, little reaction on stimuli and paleness of mucous membranes. The moderate cases showed staggering, slight cyanosis of mucous membranes and weak pulse in addition to mild cases. Moreover, prostration, dyspnea and coldness of skin were shown in severe cases (Table 2). The mild and moderate cases recovered the pre-administration state in 1 or 2 hr after onset of the reaction, and the severe cases by 2 to 4 hr without any treatment. However, some severe cases still showed slight inactivity and anorexia at

Table. 1. Incidence of shock-like reaction in dogs induced by milbemycin D administration

Dose (mg/kg)	Uninfected	Infected		Total
		mf negative	mf positive	
5	0/14 (0%)	1[a)]/25 (4%)	3/ 24 (13%)	4/ 63 (6%)
1	0/47 (0)	0 /30 (0)	12/ 97 (12)	12/174 (7)
0.2			2/ 3 (67)	2/ 3 (67)
0.1			2/ 3 (67)	2/ 3 (67)
Total	0/61 (0)	1 /55 (2)	19/127 (15)	20/243 (8)

a) Mf detected in liver and lungs on histopathological examination.

24 hr post-administration.

Electrocardiogram and clinical data exhibited no significant differences in the reaction intensity, so they were shown together in the following description. Electrocardiogram findings are summarized in Table 3. Slight or severe sinus arrhythmia was detected at pre-administration in 8 of 11 cases. These arrhythmias disappeared or were relieved at the reaction and reappeared at 6 or 24 hr on electrocardiogram. Atrial, junctional, or ventricular premature beat occurred at the reaction, 6 and 24 hr post-administration in 2, 3 and 3 cases, respectively. Types of premature beat were occasional, multifocal, variable coupling and short runs, and these types changed at the time examined in the same dog. In some dogs with premature beat, arrhythmia and systolic murmur were recognized on auscultation, and filarid-worm echoes were detected at the tricuspid valve orifice on

Table. 2. Clinical signs in dogs with shock-like reaction induced by milbeymycin D administration

Intensity of reaction	No. of dogs	Clinical Sign										
		Depression	Paleness and/or cyanosis of mucous membrane	Weak pulse	Arrythmia	Rough vesicular breath sound	Dyspnea	Skin coldness	Vomiting	Active peristalic sound	Staggering	Prostration
Mild	5	5	4	0	1	2	0	0	1	1	0	0
Moderate	3	3	3	2	0	2	1	1	2	2	3	0
Severe	12	12	12	10	2	12	9	5	4	7	12	12

Table. 3. Electrocardiogram findings in dogs with shock-like reaction induced by milbemycin D administration

Finding		Pre-administration (n=11)	Post-administration		
			At reaction[a] (n=11)	6 hr (n=10)	24 hr (n=11)
Arrhythmia	±[b]	1[c]	3	1	1
	+	3	1	2	4
	++	3	1	2	3
	+++	1	0	1	1
	Total	8	5	6	9
Premature beat		0	2	3	3
Sagging and/or slur of ST segment		1	7	6	1
Inversion of T wave			6	6	0
Height of R wave in II lead (mV)		9.0±4.7[d]	10.3±4.7*[e]	10.9±4.6*	9.2±4.9

a) At detected shock-like reaction.
b) Grade of arrhythmia, ±··detected barely irregular R-R intervals by measuring, +··detected barely irregular R-R intervals by naked eye, ++··detected distinctly irregular R-R intervals by naked eye, +++··detected severely irregular R-R intervals by naked eye.
c) Number of dogs.
d) Mean±standard deviation.
e) Significantly different from pre-administration at $P<0.05$.

two-dimensional echocardiogram at that time. Mean height (mV) of the R wave significantly increased, the ST segment sagged from 0.1 to 0.3 mV and/or was slurred in 7 of 11 cases, and the T wave was inverted in 6 of 11 cases at the reaction and after 6 hr.

Clinical data in the dogs with shock-like reaction are shown in Table 4. Mean values of body temperature, respiratory rate and heart rate did not significantly change throughout the examination. However, heart rate decreased by 50 to 90% of pre-administration level in 12 cases and increased by 110 to 170% in 4 cases. Mean value of systolic blood pressure significantly decreased at the reaction, falling to from 40 to 86% of pre-administration level in all dogs; it reached unmeasurable limitation levels (under 50 mmHg) of the hemodynameter in 5 cases.

RBC count increased at the reaction and 6 hr post-administration, but decreased at 24 hr. WBC count decreased at the reaction, increased at 6 hr post-administration, and recovered at 24 hr. WBC count was followed by neutrophil count. Eosinophil count and serum total protein (T.P) concentration decreased at the reaction and at 6 hr post-administration, and tended to recover at 24 hr. But A/G ratio, serum osmolality, sodium and potassium concentrations did not change throughout the examination.

Mean serum GOT, GPT and ALP activities increased considerably at 24 hr. Serum glucose concentration temporarily increased at the reaction. The circulating mf count at pre-administration varied from 0 to 28250 per 200 μl of blood in individual dog. It gradually decreased post-administration and reached one-twelfth of the pre-administration level at 24 hr post-administration. Mf count at pre-administration and their decrease rate at

Table 4. Clinical values in dogs with shock-like reaction induced by milbemycin D administration

Item	Pre-administration		Post-administration					
			At reaction[b]		6 hr		24 hr	
	No.[a]	Mean±SD	No.	Mean±SD	No.	Mean±SD	No.	Mean±SD
Body temperature (°C)	20	38.9 ± 0.5	20	38.6 ± 0.7	11	38.5 ± 0.8	19	39.1 ± 0.6
Respiratory rate (/min)	15	31.4 ± 10.1	15	42.5 ± 20.6	8	32.6 ± 10.9	15	32.7 ± 10.9
Heart rate (/min)	20	126 ± 22	20	118 ± 30	11	129 ± 27	19	119 ± 25
Systolic blood pressure (mmHg)	18	130 ± 14	18	74 ± 22***[c]	9	104 ± 28*	18	118 ± 22
RBC ($\times 10^4/\mu l$)	20	646 ± 126	20	712 ± 131*	11	777 ± 136*	19	610 ±134*
WBC ($\times 10^2/\mu l$)	20	128 ± 31	20	86 ± 35**	10	156 ± 27**	19	133 ± 48
Eosinophil ($\times 10^2/\mu l$)	20	10.2 ± 9.1	20	2.2 ± 2.3**	10	2.6 ± 2.4**	19	5.0 ± 6.3
Neutrophil ($\times 10^2/\mu l$)	20	92.0 ± 33.1	20	63.5 ± 33.7	10	133.4 ± 26.9**	19	104.6 ± 44.0
Lymphocyte ($\times 10^2/\mu l$)	20	22.8 ± 17.0	20	19.3 ± 9.4	10	17.0 ± 7.2	19	20.6 ± 3.2
Monocyte ($\times 10^2/\mu l$)	20	3.8 ± 2.7	20	1.1 ± 1.2	10	3.7 ± 1.9	19	2.9 ± 1.7
Serum total protein (g/dl)	19	6.72± 0.64	19	5.83± 0.67***	11	5.85± 0.69***	19	6.24± 0.42**
A/G ratio	19	0.91± 0.23	19	0.92± 0.24	19	0.93± 0.29	19	0.95± 0.24
Serum osmolality (mOsm/kg)	9	295 ± 10	9	297 ± 10		NM[d]	9	291 ± 13
Sodium (mmol/l)	7	147.4 ± 4.3	7	146.4 ± 2.9		NM	7	143.8 ± 5.7
Potassium (mmol/l)	7	4.2 ± 0.7	7	3.8 ± 0.6		NM	7	4.0 ± 0.6
GOT (IU/l)	9	41 ± 18	9	112 ± 136		NM	9	178 ±206
GPT (IU/l)	9	52 ± 46	9	99 ± 153		NM	9	377 ±603
ALP (IU/l)	9	83 ± 38	9	98 ± 46		NM	9	198 ± 86
Glucose (mg/dl)	6	94.3 ± 8.8	6	130.2 ± 22.7		NM	6	102.9 ± 15.6
Microfilaria (/200 μl)	11	6316 ±7979	11	3776 ±3759**	11	1729 ±2187***	19	510 ±726***

a) Number of dogs.
b) At detected shock-like reaction.
c) Signigicantly different from pre-administration: * $P<0.05$, ** $P<0.01$, *** <0.005.
d) Not measured.

post-administration were not related to the reaction intensity.

No abnormal clinical signs were noted in all cases at post administration in the second and third trials. Although serum T.P decreased at 3 and 6 hr in both trials and WBC count increased at 6 hr in the third trial, there were no significant differences in other clinical data between the pre- and post-administration values (Tables 5 and 6). Eosinophil count tended to decrease at post-administration in both trials, but there

Table 5. Clinical values on second administration of milbemycin D in dogs with shock-like reaction at the first administration

Item	Pre-administration		Post-administration					
			3 hr		6 hr		24 hr	
	No.[a)]	Mean±SD	No.	Mean±SD	No.	Mean±SD	No.	Mean±SD
Body temperature (°C)	7	38.6 ± 0.3	7	38.7 ± 0.7	7	38.4 ± 0.3	7	38.5 ± 0.3
Respiratory rate (/min)	6	26 ± 3	6	27 ± 6	6	39 ± 8	6	32 ± 5
Heart rate (/min)	7	101 ± 27	7	104 ± 18	7	101 ± 23	7	99 ± 27
Systolic blood pressure (mmHg)	7	123 ± 10	7	115 ± 11	7	127 ± 12	7	127 ± 15
RBC ($\times 10^4/\mu l$)	7	608 ±119	7	588 ± 118	7	588 ± 97	7	598 ±119
WBC ($\times 10^2/\mu l$)	7	146 ± 16	6	142 ± 35	6	139 ± 38	7	148 ± 42
Eosinophil ($\times 10^2/\mu l$)	7	18.9 ± 7.8	6	11.3 ± 8.9	6	11.8 ± 11.4	7	13.7 ± 13.8
Neutrophil ($\times 10^2/\mu l$)	7	96.6 ± 12.7	6	104.2 ± 26.2	6	98.0 ± 30.2	7	93.1 ± 28.6
Lymphocyte ($\times 10^2/\mu l$)	7	27.4 ± 13.7	6	27.3 ± 17.2	6	24.0 ± 19.2	7	29.4 ± 14.2
Monocyte ($\times 10^2/\mu l$)	7	3.6 ± 2.1	6	3.3 ± 1.5	6	2.8 ± 2.5	7	3.9 ± 1.7
Serum total protein (g/dl)	7	6.31± 0.30	7	5.83± 0.4*[b)]	7	5.97± 0.40*	7	6.32± 0.32
A/G ratio	7	0.99± 0.15	7	1.05± 0.16	7	1.03± 16	7	0.87± 0.10
GPT (IU/l)	7	38.4 ± 22.2		NM[c)]		NM	7	48.8 ± 30.6
Glucose (mg/dl)	7	84.2 ± 14.2	7	86.1 ± 13.2		NM	7	95.0 ± 6.2
Microfilaria (/200 μl)	7	596 ±947	7	5845 ±1050	7	293 ±487	7	226 ±405

a) Number of dogs.
b) Significantly different from pre-administration at $P<0.05$.
c) Not measured.

Table 6. Clinical values on third administration of milbemycin D in dogs with shock-like reaction at the first administration

Item	Pre-administration		Post-administration					
			3 hr		6 hr		24 hr	
	No.[a)]	Mean±SD	No.	Mean±SD	No.	Mean±SD	No.	Mean±SD
Body temperature (°C)	5	38.4 ± 0.3	5	38.4 ± 0.2	5	38.5 ± 0.2	5	38.4 ± 0.2
Respiratory rate (/min)	5	25 ± 8	5	26 ± 6	5	31 ±11	5	28 ± 9
Heart rate (/min)	5	101 ± 25	5	100 ± 29	5	106 ± 33	5	108 ± 19
Systolic blood pressure (mmHg)	5	124 ± 12	5	117 ± 17	5	127 ± 16	5	129 ± 11
RBC ($\times 10^4/\mu l$)	5	582 ±102	5	582 ±106	5	576 ±114	5	558 ±118
WBC ($\times 10^2/\mu l$)	5	118 ± 40	5	103 ± 18	5	135 ± 39*[b)]	5	127 ± 33
Eosinophil ($\times 10^2/\mu l$)	5	15.8 ± 6.1	5	10.6 ± 10.8	5	7.8 ± 3.4	5	10.6 ± 3.8
Neutrophil ($\times 10^2/\mu l$)	5	69.4 ± 24.2	5	71.6 ± 16.9	5	95.6 ± 35.9	5	88.6 ± 33.9
Lymphocyte ($\times 10^2/\mu l$)	5	28.0 ± 18.5	5	21.6 ± 10.1	5	19.8 ± 12.1	5	22.0 ± 10.0
Monocyte ($\times 10^2/\mu l$)	5	3.2 ± 3.9	5	2.8 ± 1.1	5	3.2 ± 1.3	5	2.4 ± 1.3
Serum total protein (g/dl)	5	6.22± 0.26	5	5.88± 0.42*	5	6.02± 0.30*	5	6.14± 0.25
A/G ratio	5	0.93± 0.15	5	0.95± 0.19	5	0.94± 0.19	5	0.82± 0.21
GPT (IU/l)	5	37.4 ± 14.9		NM[c)]		NM	5	45.9 ± 27.7
Microfilaria (/200 μl)	5	221 ±286	5	162 ±124	5	55 ± 52	5	26 ± 22

a) Number of dogs.
b) Significantly different from pre-administration at $P<0.05$.
c) Not measured.

were no statistically significant changes. Mf counts at pre-administration in the second and third trials were considerably lower than in the first trial, and decreased to about one-third of pre-administration level in the second trial and one-ninth in the third trial at 24 hr post-administraion.

DISCUSSION

The main clinical findings in the shock-like reaction by Milbe (Milbe reaction) were depression, paleness and/or cyanosis of the visible mucous membranes, weak pulse, staggering, prostration and remarkable fall of blood pressure. These findings essentially agreed with those in the shock-like reaction by DEC (DEC reaction). However, it seemed that the Milbe reaction was slighter than the DEC reaction, for lethality of the DEC reaction (10%) [13, 15] was higher than the Milbe reaction (0%).

It is generally known that the heart rate increases in order to compensate for the decrease of circulating blood volume in shock. Actually, the heart rate increased in the DEC reaction [1, 15], but it tended to decrease in many cases in the Milbe reaction. This might be attributable to the pharmacological action of Milbe [16]. Arrhythmia occurred after Milbe administration in uninfected dogs (unpublished data), but the arrhythmia which was seen at pre-administration disappeared or was relieved at the Milbe reaction. Since it is known that sinus arrhythmia in healthy dogs disappears by atropin [9], anticholigenic substances might be involved in the Milbe reaction, but heart rate did not increase. In this way, the changes of the cardiac function in the Milbe reaction were complecated and difficult to explain. Premature beat was seen at the reaction and/or after it in some cases, but not in uninfected and infected dogs without the shock-like reaction, except for dogs with dirofilarial hemoglobinuria (caval syndrome). Heartworm migration from the pulmonary arterial trunk to the tricuspid valve orifice occurred, and premature beat appeared to be accompanied with heartworm migration in dirofilarial hemoglobinuria developing after Milbe administration [12]. In a few cases with premature beat in the Milbe reaction, heartworm was also detected at the tricuspid valve orifice, so it was suggested that the premature beat resulted from heartworm stimulation for the heart wall.

RBC count decreased, but WBC count and WBC component did not change post-administration in a dose of 1 or 5 mg/kg of Milbe in uninfected dogs [16]. In the Milbe reaction, RBC count increased at the reaction and 6 hr, total WBC and neutrophil counts decreased at the reaction and increased at 6 hr, and eosinophil count decreased at the reaction, as well as at 6 and 24 hr. These hematological changes virtually agreed with the DEC reaction [2, 13–15]. Serum T.P in the Milbe reaction decreased with the same pattern as in uninfected dogs, but it did not change [2, 7], or decrease [13, 14] in the DEC reaction. It was suspected that these hematological and biochemical changes resulted from interaction of pharmacological action of the drug and the substance inducing the reaction.

In the DEC reaction, serum enzyme activities mostly increased at the reaction [2, 7, 13–15], and this reaction has been considered to be caused by damage to the liver cells or by accelerating the liver cell membrane permeability [2, 7, 15]. On the other hand, those in the Milbe reaction increased at 24 hr, and this reaction may depend on damage to th liver cells followed by killing of mf. Increased serum glucose concentraion at the reaction might reflect an increased serum glucocorticoid concentration.

Some investigators have reported that the intensity of the DEC reaction depends on

circulating mf count at pre-administration [7, 14, 15]. However, the mf count was not related to the Milbe reaction in this study; for example, a case in which mf could not be detedcted in peripheral blood had the reaction, and many cases in which over 10,000 were detected per 200 μl of blood did not have the reaction [16]. In a circulating mf negative case with the reaction, mf were detected in the liver and lungs on histopathological examination (unpublished data), and the shock-like reaction did not occur in the mf negative and uninfected dogs. Therefore, killing mf after administration might play an important role in the Milbe reaction.

It was suspected that the mechanism of the Milbe reaction might be the same as in the DEC reaction, because the clinical symptoms and data were similar in both reactions. The mechanisms of the DEC reaction on onchocerciasis in human and on heartworm disease in dogs have been studied by many investigators. The majority indicated that some immunological mediators triggered the DEC reaction [3, 5–8, 10, 14, 15, 17, 18], and some considered eosinopenia in the DEC reaction to be one evidence of immunological reactions [3, 8, 10]. Eosinopenia was also noted in the Milbe reaction. Although eosinopenia might be due to an influence of glucocorticoids, it seemed that the Milbe reaction was involved in some immunological reactions. The DEC reaction recurred when the drug was repeatedly administered [2, 7, 15], but the Milbe reaction did not recur. This disagreement suggested that there might be a little difference in mechanism of the shock-like reaction between Milbe and DEC.

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要　約

犬糸状虫予防薬ミルベマイシンDの臨床応用：ショック様反応発症犬の臨床所見：佐々木栄英，北川　均，石原勝也（岐阜大学農学部家畜内科学講座）——犬糸状非寄生犬および寄生犬243頭に0.1～5 mg/kg のミルベマイシンDを1回経口投与したところ，末梢血中（19頭），または病理組織学的（1頭）にミクロフィラリア（mf）が検出された寄生犬20頭（8％）でショック様反応が認められた。投薬後24時間の mf 数は投与前の1/12に減少していたが，投薬前の末梢血 mf 数または投薬後の mf 減少率と発症の有無および症状の強さとの間には関連性がなかった。臨床症状は，投薬1.5～4時間後に発生し，1～4時間続いた後，全例回復した。症状は元気消失，可視粘膜の蒼白またはチアノーゼ，弱脈，皮膚の冷感，呼吸困難，歩様蹌踉，虚脱，心拍数の減少傾向，血圧の著しい低下など循環不全に基づく所見が主体であった。発症時の心電図検査では，不整脈の消失または軽減，R波の増高，ST部の低下およびT波の逆転などが認められた。血液所見では，赤血球数の増数，好中球の変動に伴う白血球数の早期における減数と後期における増数，好酸球の減数，血清総蛋白濃度の低下，血糖値の上昇などがみられ，血清酵素活性値は24時間後に上昇していた。再投与および再々投与では，実験犬は臨床的異常を示さなかった。