イヌにおける2-sec-butylphenyl N-methylcarbamate (BPMC) の急性毒性に及ぼすO,O-dimethyl()- (3methy-4-methylthiophenyl) phosphorothioate（フェンチオン）前処理による影響

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Effect of *O, O*-Dimethyl *O*-(3-methyl-4-methylthiophenyl) Phosphorothioate (Fenthion) Pretreatment on Acute Toxicity of 2-*sec*-Butylphenyl *N*-Methylcarbamate (BPMC) in Dogs

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The combinations of *O,O*-dimethyl *O*-(3-methyl-4-nitrophenyl) phosphorothioate (fenitrothion) or *O,O*-dimethyl *O*-(3-methyl-4-methylthiophenyl) phosphorothioate (fenthion) with 2-*sec*-butylphenyl *N*-methylcarbamate (BPMC) are used in large quantities in Japan to control plant hoppers and leaf hoppers in rice plants.

Recently, we reported that acute toxicity of BPMC was potentiated to 5- or 10-fold in mice by the pretreatment with fenitrothion [4, 5] or fenthion [2, 3], respectively. These reports suggested that the inhibition of detoxication of BPMC by the thiophosphates (fenitrothion, fenthion) indicating the increase of BPMC plasma level, the *in vitro, in vivo* inhibition of hepatic BPMC metabolism, and the prolongation of hexobarbital sleeping time played an important role in the potentiation. These reports also suggested that the desulfuration of the thiophosphates might be responsible for the inhibition of BPMC metabolism.

In a dog study of BPMC-fenitrothion combination, pretreatment with fenitrothion caused the increase of BPMC plasma levels and the potentiation of BPMC toxicity, but the potentiated ratio was smaller than that in mice and the mechanism was not elucidated [1]. If the mechanism of the potentiation of BPMC toxicity in dogs would be similar to that in mice, it was of interest how the relationship between the inhibition of BPMC metabolism caused by the thiophosphates and the potentiation of BPMC toxicity would be. In the present study, therefore, the toxicological interaction between BPMC and fenthion, which was a more active potentiator, was investigated in dogs. Effect of the desulfuration of fenthion on metabolism of BPMC was examined by comparing the effects of fenthion, fenthion sulfoxide (main metabolite of fenthion) and fenthion oxon (fenthion desulfurated metabolite) on hepatic microsomal metabolism of BPMC *in vitro*.

Male, female beagle dogs, weighing 9–12 kg, were used. The animals were fed on commercial dog food (Oriental Yeast Co., Ltd. Tokyo, Japan) 300 g/dog/day and allowed to drink *ad libitum*. Technical grade chemicals were kindly given by following companys: BPMC (99% purity); Sumitomo Chemical Co., Ltd. (Osaka, Japan), fenthion (95%), fenthion oxon (94%); Nihon Tokushu Noyaku Seizo K.K. (Tokyo, Japan). Fenthion sulfoxide (99%) was purchased from Wako Pure Chemical Industries, Ltd. (Tokyo, Japan).

BPMC and fenthion were administered by a gelatin capsule to 20-hr fasted animals. The minimum lethal dose (MLD) of BPMC and fenthion were 800 and 600 mg/kg, respectively. They were determined by a pyramiding dosing (BPMC: 200, 400 and 800 mg/kg; fenthion: 150, 300, 600, 1200 and 2400 mg/kg). BPMC (100 mg/kg, 1/8 MLD) was administered at 1, 6, 24 hr after the pretreatment with fenthion of 150 mg/kg (1/4 MLD).

Animals were anesthetized with carbon dioxide and then sacrificed by exsanguination from the carotid artery. The livers were perfused with 1.15% KCl and removed, and the microsomes were prepared as described previously [3]. Enzyme activities were determined by the method described previously [3].

The toxic signs of BPMC poisoning were tremor, salivation and diarrhea which were similar to those observed at the previous study [1]. Four hr after the administration of 100 mg/kg of BPMC, these symptoms disappeared. The signs of fenthion poisoning such as decreased motor activity, vomiting, salivation and fasciculation were observed from 7 hr to 2 days after dosing at more than 300 mg/kg. Vomiting was only observed at 150 mg/kg of fenthion. BPMC toxicity seemed to be weakened by the 1-hr pretreatment with fenthion of 1/4 MLD (150 mg/kg), but was potentiated by the 24-hr pretreatment. The toxic signs after 6- or 24-hr pretreatment were obviously prolonged and death was observed in 2 out of 4 animals (Table 1).

Table 1. Effect of fenthion pretreatment on BPMC toxicity in dogs

Fenthion Pretreatment		BPMC (mg/kg)	Mortality	Signs	Time after BPMC treatment (hr)						
(mg/kg)	(hr)				1	2	3	4	5	7	24
0	0	100	0/2	Tremor	++[a)]	++	+	−			
				Salivation	++	+	+	−			
				Diarrhea	+	−					
150	0	0	0/2	Vomiting						+	+
	1	100	0/2	Tremor	+	+	−				
				Salivation	+	+	−				
				Diarrhea	+	−					
				Vomiting		+					+
	6	100	1/2	Tremor	+	+	+	+			
				Salivation	+	+	+	+			
				Vomiting		+					+
	24	100	1/2	Tremor	++	++	++	+	+	+	
				Salivation	+	+	++	+	+	+	
				Diarrhea	+						
				Vomiting		+					

a) −; No abnormalities detected, +; Slight, ++; Moderate.

Table 2. Effect of fenthion and its metabolites on *in vitro* BPMC metabolism by the microsomal fraction of dog liver homogenate[a)]

Treatment	Concentration (μM)	BPMC Metabolism	
		Activity	% metabolism
Fenthion	Control	26.82±1.38	100
	5	24.72±0.81	92
	25	20.13±0.28[b)]	75
	50	17.91±0.57[c)]	67
Fenthion sulfoxide	Control	26.46±1.37	100
	5	25.37±0.83	96
	25	20.83±0.72[b)]	78
	50	19.00±0.72[c)]	72
Fenthion oxon	Control	35.51±1.86	100
	5	33.85±0.36	95
	25	31.25±0.28	88
	50	33.62±0.74	95

a) Total 3 m*l* incubation mixture contained 0.3 μmoles of BPMC, various concentrations of fenthion and its metabolites, 1.5 m*l* of 2% microsomal fractions and 1.5 m*l* of 0.1 M phosphate buffer (pH 7.4) in addition to the NADPH-generating system. The incubation under air was carried out for 20 min at 37°C. Activities are expressed as the mean±S.E. (n=3) of substrate metabolized in n mol/mg protein/20 min.

b) Significantly different from control ($p<0.05$).

c) Significantly different from control ($p<0.01$).

BPMC metabolism *in vitro* was significantly inhibited dose-dependently by fenthion or the sulfoxide but not by the oxon (Table 2). These results suggested that the desulfuration of the thiophosphates (fenthion and the sulfoxide) might be responsible for the inhibition of BPMC metabolism.

From the results of acute toxicity, the pretreatment with fenthion caused the potentiation of BPMC toxicity, as that with fenitrothion [1]. It was required for the potentiation to pretreat with fenthion at least for 6 hr and the time was similar to that of onsets of fenthion toxicity. These results suggested that the metabolism or the metabolic process of fenthion played an important role in the potentiation of BPMC toxicity as well as the potentiation in mice.

The inhibitory effects of fenthion to BPMC metabolism *in vitro* in dogs was similar to that in mice, i.e., the inhibition of BPMC metabolism by fenthion or fenthion sulfoxide was observed but not by fenthion oxon. The rate of inhibition (25%) by fenthion in dogs was smaller than that (36%) in mice [4]. These results suggested that the inhibition of BPMC metabolism by fenthion might be at least in part responsible for the potentiation of BPMC toxicity in dogs.

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要　　約

イヌにおける 2 -sec-butylphenyl N-methylcarbamate（BPMC）の急性毒性に及ぼすO,O-dimethyl O-（3 -methyl- 4 -methylthiophenyl）phosphorothioate（フェンチオン）前処理による影響（短報）：宮岡貞次・津田修治・白須泰彦（残留農薬研究所）――イヌにおける BPMC とフェンチオンの急性毒性における相互作用を肝の in vitro BPMC 代謝との関連において調べた。フェンチオン 150 mg/kg（1/4最小致死量，MLD）前処置後，BPMC 100 mg/kg（1/8MLD）投与により 4 匹中 2 匹が死亡し，BPMC の中毒症状は延長された。肝ミクロゾームにおける BPMC の代謝は，フェンチオンで抑制されたが，フェンチオン　オキソンでは抑制されなかった。