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ANTICOAGULANT RODENTICIDE

Toxicity and Antidotal Studies on 2-Pivalyl-1,3-indandione (Pival), an Anticoagulant Rodenticide

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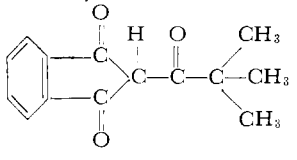
The anticoagulant properties of 2-pivalyl-1,3-indandione and the use of vitamin K preparations as antidotes for poisoning in dogs and secondary toxicity in cats have been investigated. 2-Pivalyl-1,3-indandione is a much more effective poison in small daily dosages than in single large doses. Vitamin K_1 is a more effective intravenous antidote than vitamin K. Under the conditions of this study, secondary poisoning of cats does not appear to be a significant hazard.

RAPID ACTING, single-dose poisons used to eradicate commensal rodents have always presented a serious problem in public health. The discovery of the feasibility of using anticoagulants as rodenticides has eliminated some of these hazards. The early work has been reviewed by several recent authors (*2–4, 14, 17*).

Anticoagulants, as the name implies, elicit changes in the body which reduce or prevent clotting of the blood. The effect of these compounds on the blood clotting mechanism can be measured in many ways, including determination of the prothrombin time or the coagulation time. As the anticoagulant effects become more pronounced, the prothrombin and coagulation times will become longer. If there is no treatment to correct these alterations in the blood, fatal hemorrhages will occur. The use of anticoagulants such as some dicoumarin derivatives or 2-substituted 1,3-indandiones as rodenticides takes advantage of the above facts. To be effective, these materials are incorporated in cereal baits in very low concentrations (0.025%) and made easily accessible to the rodents. After several days of feeding, hemorrhages occur and the animals die a relatively painless death. In such low concentrations, and because death results only after several feedings, anticoagulant rodenticides are advantageous in reducing acute or single-dose hazards to humans or domestic animals.

2-Pivalyl-1,3-indandione (Pival, also referred to as *tert*-butylvalone) is a typical 2-substituted 1,3-indandione prepared by reaction of pinacolone with diethyl phthalate (*8*). This compound, a bright yellow crystalline material with a very slight odor, was first synthesized and patented by Kilgore about 1937 (*7*) as one of a series of 2-acyl-1,3-indandiones. It has the following chemical structure:



2-Acyl-1,3-indandiones are active as insecticides and the optimal insecticidal effectiveness is reached when there are five carbons in the acyl radical, as in Pival (*8*). These insecticidal properties are advantageous in a compound to be incorporated in cereal baits and left open to attack by cereal-destroying insects.

Data presented were obtained from limited toxicity studies, in dogs and cats, of Pival both as the pure material and as a 0.5% mixture in an inert medium.

Methods

Healthy mongrel dogs, male and female, were selected at random. The animals had been acclimated to the laboratory environment for approximately 2 weeks, had received inoculations of rabies vaccine and anticanine distemper and antiinfectious canine hepatitis serum, and had received a vermifuge. The investigations in dogs were separated into two phases: (1) the acute toxicity of Pival, and (2) the subacute toxicity of Pival and the effectiveness of vitamin K preparations in reversing the hemorrhagic tendencies caused by Pival.

Prothrombin and coagulation times were determined before Pival was administered and at frequent intervals thereafter. Prothrombin times were determined by a modification of Quick's method (*15*).

Blood was drawn by venipuncture, mixed in a 9 to 1 ratio with 0.1*M* sodium oxalate, and centrifuged for 10 minutes at approximately 2000 r.p.m. A test tube containing 0.2 ml. of Simplastin (brand of thromboplastin extract, Chilcott Laboratories) suspension and another tube containing plasma were then incubated at 37° C. in a water bath for 6 minutes. Next, 0.1 ml. of the plasma was added to the tube containing the Simplastin, and timing was begun. The mixture was slowly stirred with a small loop of No. 22 Nichrome wire until the

end point, clot formation, was reached. Throughout these studies at least two determinations of the prothrombin times were made on each sample of blood. Averages of the two determinations are presented.

Coagulation times were determined by the Lee-White method (*9*) at the beginning of the acute studies only. For the remainder of the investigations the capillary tube method (*11*) was employed.

The literature (*1, 12, 13, 19*) and experience in this laboratory indicate that prothrombin times of from 7 to 12 seconds, using undiluted plasma, and coagulation times of from 1 to 5 minutes are within normal limits in dogs. It was therefore arbitrarily decided that prothrombin times above 20 seconds and coagulation times above 8 to 10 minutes could elicit bleeding tendencies and were dangerous levels, and that antidotal studies would be initiated when the prothrombin times reached 60 seconds and coagulation times were 8 minutes or above.

At the end of each study all surviving animals were sacrificed by the intravenous administration of 100 mg. of sodium pentobarbital per kg. Complete gross autopsies were performed on all animals which died during the course of these studies or were sacrificed at termination.

Toxicity Studies on Dogs

Acute Toxicity Pure Pival was administered by capsule to two dogs at 25 mg. per kg., four dogs at 75 mg. per kg., and two dogs at 100 mg. per kg. One additional dog received by stomach tube 5 grams per kg. of the 0.5% Pival rodenticide concentrate suspended in 5% acacia water, a total dosage of 25 mg. of Pival per kg. Each dog was closely observed during the entire experimental period for gross signs of systemic toxicity. Prothrombin and coagulation times were determined prior to the administration of Pival, and daily thereafter until death or recovery.

When marked toxic signs developed 1 mg. of vitamin K_1 (Mephyton, 2-methyl-3-phytyl-1,4-naphthoquinone, Merck & Co., Inc., Rahway, N. J.) per kg. was injected intravenously into two dogs of the 25 mg. per kg. level. No antidote was given to the remaining animals.

Within a short time following the single oral doses of Pival, all dogs exhibited some lengthening of prothrombin and coagulation times (Tables I and II). Within 4 to 6 days these times had reached their maxima in dogs that had received 25 mg. of Pival per kg., and either returned slowly to normal, in the untreated dog, or were normal within 20 hours in the two dogs to which were administered 1 mg. of vitamin K_1 per kg. In the 75 mg. per kg. dogs the prothrombin and coagulation times gradually increased to reach their maxima in 11 days, then slowly returned to normal levels. One animal in this group died within 24 hours. No toxic symptoms were observed on this dog prior to death, which occurred during the night. Autopsy, however, revealed many evidences of a hemorrhagic death. Both dogs on the 100 mg. per kg. level showed consistent rises in prothrombin and coagulation times until death on the third and eighth day, respectively.

Gross signs of systemic toxicity among the dogs receiving the single oral doses of Pival were weakness, anorexia, bleeding at the sites of venipuncture, and, in the 100 mg. per kg. level, salivation, vomiting, bloody fluid in the mouth, bloody feces, and progressive weakening until death. The weakening was accompanied by an apparently increased general muscle tonus.

Post-mortem examination in all animals revealed a high incidence of subcapsular cortical infarcts in the

Table I. Daily Prothrombin Times (in Seconds) in Mongrel Dogs Following Oral Administration of Pival

Days	C-140 M	C-141[a] M	C-142 F	C-140 M	C-142 F	C-150 F	C-151 F	C-165 M	C-16 M
	25 Mg./Kg.			75 Mg./Kg.				100 Mg./Kg.	
0–1	11.8	10.2	9.6	...	...	...	7.7	8.6	8.2
0	11.2	9.5	8.4	7.6	7.1	7.5	10.0	8.8	8.3
1	15.7	15.6	11.6	12.2	12.1	Dead	16.1	17.9	18.3
2	25.1	32.3	22.5	20.9	19.5		27.4	44.6	44.6
3	17.5	49.1	25.7	29.1	38.7		36.5	80.0	Dead
4	32.3	873.4	27.6	43.3	71.2		91.3	197.4	
5	41.6	33.6	20.2	47.2	115.4		30.5	94.4	
6	71.4[b]	37.2	35.9	39.5	116.4		32.5	139.8	
7	8.0	34.1	26.7	63.2	153.6		19.5	307.8	
8	7.9	14.5	33.5	75.9	266.5		S	Dead	
9	8.9	9.9	35.5	31.5	221.3				
10		7.8	31.9	...	...				
11		...	25.5[b]	540+	540+				
12		...	7.7	...	...				
13		...	10.6	...	...				
15		...		47.5	45.3				
16		...		25.5	21.2				
17		...		17.4	22.0				
18		...		13.2	15.6				
19		...		11.5	13.3				
21		...		9.0	11.3				
22		Dead		8.7	13.5				
				S	S				

[a] Administration of Pival rodenticide concentrate orally by stomach tube.
[b] Administration of 1 mg./kg. vitamin K_1.
S. Sacrificed.

Table II. Daily Coagulation Times (in Minutes) in Mongrel Dogs Following Oral Administration of Pival

(Times calculated to nearest 15 seconds)

Days	C-140 M	C-141[a] M	C-142 F	C-140 M	C-142 F	C-150 F	C-151 F	C-165 M	C-166 M
	25 Mg./Kg.			75 Mg./Kg.				100 Mg./Kg.	
0	1.5	1.25	1.75	1.75	1.0	3.25	2.25	2.75	1.0
1	2.5	1.5	2.5	4.25	2.25	Dead	2.75	2.25	2.75
2	2.25	3.25	2.75	3.25	3.5		3.5	5.25	5.25
3	3.75	4.75	3.5	3.25	1.5		3.75	2.75	Dead
4	...	...	...	4.5	4.5		3.25	4.25	
5	...	5.5	...	4.25	5.5		5.25	6.0	
6	[b]	3.5	...	3.5	6.75		4.75	5.25	
7	...	3.5	...	3.25	7.5		2.75	5.5	
8	...	2.75	...	7.5	4.25		S	Dead	
9	2.25	...	5.0	4.25	7.75				
11		...	12.5[b]	3.25	7.0				
12		...	1.0						
13		...	9.75						
15		...		6.5	8.0				
16		...		2.5	5.5				
17		...		3.25	4.5				
18		...		2.5	4.75				
19		...		2.25	3.25				
21		..		2.25	4.25				
22		Dead		1.0	3.5				
				S	S				

[a] Administration of Pival rodenticide concentrate orally by stomach tube.
[b] Intravenous injection of 1 mg./kg. vitamin K_1.
S. Sacrificed.

kidneys, irritation of the gastrointestinal tract, and hemorrhages in the lungs. Most of the animals that succumbed during the experimental period exhibited some vascularization or hemorrhages involving the brain and its coverings.

Subacute Toxicity and Antidotal Studies Ten dogs were used in these studies, divided into a control group (two dogs), and an experimental group (eight dogs). All dogs were fed a daily bait of horse meat calculated to be equivalent to 1% of the body weight of the animal. For the experimental dogs each bait contained 0.025% Pival by weight; this amounted to the oral ingestion of 2.5 mg. per kg. per day. The regular laboratory diet and water were offered *ad libitum* to each dog after the bait had been consumed.

Prothrombin and coagulation times were determined initially and followed closely after the animals had started on the bait. Two experimental animals were fed the Pival baits each day until death. All other animals received baits until definite toxic signs of markedly prolonged prothrombin and coagulation times developed, at which time the bait was withdrawn. Two of this latter group of dogs then were given intravenously 1 mg. of vitamin K_1 per kg., two received, over a period of 48 hours, several intravenous doses of Synkayvite Roche (tetrasodium salt of 2-methyl-1,4-naphthohydroquinone disphosphoric acid), a synthetic vitamin K compound, and the remaining two animals received no other treatment than the removal of the bait.

Tables III and IV present the prothrombin and coagulation times of the dogs on the subacute study. These times increased progressively up to the sixth day of the study in all but one dog, No. C-146, where the peak was not reached until about the eleventh day.

Of the dogs in group 1 which remained on the Pival bait until death, No. C-149 received a total of 15 mg. of the compound per kg. and died on the seventh day of the study, while the other dog received a total of 32.5 mg. per kg. and succumbed on the thirteenth day of the experiment.

The remaining six experimental dogs in groups 2, 3, and 4 each had ingested a total of 17.5 mg. per kg. of Pival when the bait was removed. At that time, all animals had prothrombin times and coagulation times well above normal values. One of the dogs (C-147) in group 4 which was given 1 mg. of vitamin K_1 per kg. intravenously had normal prothrombin and coagulation time values within 24 hours, while the other dog (C-148) showed a slower return of these values to normal, during the week following the vitamin K_1 injection.

The intravenous administration of 1 mg. per kg. of Synkayvite Roche to the dogs of group 3 (Tables III and IV) decreased the prothrombin and coagulation time values in 24 hours. The decrease in prothrombin time was very slight in dog C-145; therefore, this animal was injected with another 1 mg. per kg. dose of Synkayvite Roche. Gross signs of systemic toxicity and hemorrhages did not subside appreciably during the first 24 hours following the administration of Synkayvite Roche and within 48 hours the coagulation times had increased to 18 and 25.5 minutes in dogs C-145 and C-152, respectively (Table IV). Each dog was then given 10 mg. per kg. of Synkayvite Roche intravenously. The coagulation and prothrombin times fluctuated somewhat in these animals for the next 5 days, but then dropped to within normal limits.

The dogs in group 2, which received no treatment except the removal of Pival bait, did not recover. Prothrombin and coagulation times decreased somewhat following the removal of Pival, but both dogs died within a week.

Gross signs of systemic toxicity in these animals were generally the same as those observed following the acute administration of Pival, with the additional signs of labored respiration, tremors, extensor spasms, and coma in animals that died from the effects of Pival.

Autopsy findings were also generally the same as in the acute phase animals.

Secondary Toxicity Studies on Cats

The secondary toxicity hazards of Pival were studied by feeding cats Pival-poisoned mice.

A diet containing 0.025% Pival in ground rat meal was prepared and offered to 40 male albino mice housed collectively. The diet and water were available at all times. When signs of bleeding were apparent in some of the mice and at least one death had occurred, all surviving mice were sacrificed, weighed, frozen with liquid air or dry ice, and homogenized in a Waring Blendor with 1000 ml. of distilled water. The homogenate was then frozen in an ice cube tray.

Three cats were selected and control coagulation times of blood taken from a slit in the ear pinna were determined, by the capillary tube method. One cat was designated as a control and was given one normal live mouse each day. Each of the two other cats received aliquots

Table III. Prothrombin Times (in Seconds) of Mongrel Dogs Following the Daily Ingestion of Bait (1% of Body Weight) Containing 0.025% Pival

[Group 1 received Pival until death. Pival was withdrawn after 6 days in Groups 2, 3, and 4. After Pival withdrawal, vitamin K (Synkayvite Roche) was administered intravenously to Group 3 and Vitamin K_1 (Mephyton) to Group 4]

	C-150	C-151	C-146	C-149	C-153	C-154	C-145	C-152	C-147	C-148
	F	F	M	F	M	M	M	F	M	F
Days	Controls		Group 1		Group 2		Group 3		Group 4	
0–1	7.7	7.9	8.1	7.0	7.4	7.1	7.6	7.9	7.7	7.4
0	8.5	9.1	8.6	8.4	9.0	8.6	8.6	9.4	8.7	8.4
3	19.7	11.8	21.3	24.9	32.0	28.4	17.4	23.5	15.8	22.6
5	16.5	8.4	14.5	79.8	42.9	35.0	51.6	18.2	40.4	88.2
6	9.9	8.2	18.0	139.4	128.7	128.3	65.5[a]	720–840[a]	60.6[a]	1200[a]
							Pival Discontinued			
7	8.7	8.1	28.1	Dead	39.3	42.4	62.5[a]	17.6	10.6	14.7
8	7.9	7.7	23.8		39.9	18.7	19.0[b]	19.7[b]	10.3	24.7
9	7.6	8.1	55.5		28.1	31.9	47.2	15.1	11.5	26.8
10	7.6	7.8	16.8		34.0	32.9	18.9	16.8	11.6	22.1
11	...	...	80.6		83.4	Dead	17.1	22.2	10.1	24.7
12	7.5	7.7	35.0		28.0		9.6	10.7	7.8	15.2
13			Dead		Dead		26.5	...	...	9.4
14							7.6	8.4	...	17.7
16							8.6	9.4	10.4	12.7
							S	S	S	S

[a] Intravenous injection of antidote (1 mg./kg.).
[b] Intravenous injection of antidote (10 mg./kg.).
S. Sacrificed.

Table IV. Coagulation Times (in Minutes) of Mongrel Dogs Following Daily Ingestion of Bait (1% of Body Weight) Containing 0.025% Pival

(Group 1 received Pival until death. Withdrawal of Pival after 6 days in Groups 2, 3, and 4 was followed by vitamin K administration to Group 3 and vitamin K_1 to Group 4)

Days	C-150 F Controls	C-151 F Controls	C-146 M Group 1	C-149 F Group 1	C-153 M Group 2	C-154 M Group 2	C-145 M Group 3	C-152 F Group 3	C-147 M Group 4	C-148 F Group 4
0	1.0	1.5	2.5	1.5	2.0	2.0	1.25	1.25	2.0	1.5
3	4.75	4.0	3.5	7.0	3.75	3.25	3.25	3.25	3.5	8.0
5	2.0	1.0	2.0	15+	8.0	4.75	6.5	4.0	5.0	5.0
6	1.25	1.75	3.0	25.5	10.0	8.0	14.0[a]	18.0[a]	8.0[a]	11.0[a]
					Pival Discontinued					
7	2.25	1.0	5.75	Dead	13.0	7.0	6.5[a]	5.75	1.5	3.5
8	1.0	1.0	7.0		9.0	12.0	18.0[b]	25.5[b]	1.5	3.75
9	1.5	2.25	12.0		4.75	3.0	20.0	2.5	1.0	2.5
10	1.0	3.0	10.5		4.25	12.0	1.5	4.75	3.0	4.25
11	...	...	16.0		9.5	Dead	4.0	4.75	1.0	3.5
12	3.25	3.75	27.5		10.5		3.0	4.75	3.25	3.5
13			Dead		Dead		1.5	...	...	4.5
14							2.25	3.5	...	4.0
16							2.5	2.5	4.0	2.25
							S	S	S	S

[a] Intravenous injection of antidote (1 mg./kg.).
[b] Intravenous injection of antidote (10 mg./kg.).
S. Sacrificed.
Determination on 0 day by Lee-White method. Other determinations by capillary tube method.

of the whole mouse homogenate, equivalent to one 25-gram mouse, for 13 days and portions equal to two mice for 2 days. The mouse homogenate was mixed with a small amount of commercial cat food. Additional cat food was offered *ad libitum* daily. Coagulation times of each cat were determined at 3-day intervals for the first 12 days and on the fourteenth day of the study. The cats were observed daily for gross signs of systemic toxicity and bleeding tendencies. After 15 days the cats were sacrificed, blood was collected for prothrombin and coagulation times, and complete gross autopsies were performed.

In the mice fed the 0.025% Pival diet, Pival intoxication was apparent within 24 hours, when they exhibited signs of weakness and gross bleeding from the anus. After 48 hours one mouse had died and it became apparent that the animals had ingested nearly the maximum tolerable amount of the compound.

In the cats receiving portions of the Pival-poisoned mouse homogenate, no untoward effects were found. Both remained healthy, with no significant changes in coagulation times over the 15-day period. Terminal coagulation and prothrombin times of the experimental and control animals were comparable.

At autopsy, no significant gross pathology was found which could be directly attributed to secondary Pival intoxication.

Discussion and Conclusions

Under the test conditions, Pival is an effective anticoagulant. These effects are cumulative, as indicated by the continuous rise in prothrombin and coagulation times. Pival is a much more effective poison in small daily dosages than in single large doses. In these studies, the acute oral lethal dose of Pival is on the order of 75 to 100 mg. per kg. in dogs; the subacute lethal dose is approximately 15 to 35 mg. per kg., when administered in small daily doses of 2.5 mg. per kg. Autopsy findings show that death is due mainly to hemorrhagic manifestations.

Vitamin K_1, as many investigators (*5, 6, 10, 16, 18*) have found, is a more effective intravenous antidote in hypothrombinemia than is the water-soluble vitamin K compound, Synkayvite Roche. Vitamin K_1 elicited a more rapid decrease of the prolonged prothrombin and coagulation times in single intravenous doses of 1 mg. per kg., as compared to a relatively slow, fluctuating decrease in prothrombin and coagulation times in dogs receiving 11 and 12 mg. per kg. of vitamin K intravenously. However, in one dog receiving 1 mg. per kg. of vitamin K_1 there was a rapid decrease of prothrombin and coagulation times followed by a transient rise.

The limited studies on secondary toxicity in cats were included as a demonstration of a unique method of evaluating hazard to domestic animals upon ingestion of Pival-poisoned rodents. The results were indicative that secondary hazard would be unlikely under conditions of use. A more thorough investigation would be required to confirm this assumption.

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