Bull. Environm. Contam. Toxicol. 30, 122–126 (1983)

Comparative Acute Oral Toxicity of *para*-Aminopropiophenone (PAPP) in Mammals and Birds

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For several years the Denver Wildlife Research Center has been evaluating toxicants as potential agents for reducing coyote predation on cattle, sheep, goats, and poultry. Some of the chemicals tested include sodium cyanide, mandelonitrile, 4-aminopyridine, phosphamidon, diphacinone, and sodium monofluoroacetate (Compound 1080) (CONNOLLY et al. 1978). One of the testing objectives has been to develop chemicals that are selectively toxic to coyotes. The source for the majority of chemicals tested has been through personal communications and references. To avoid a major screening effort with coyotes, and since coyotes and dogs belong to the canid family and would presumably be similar physiologically, initial screening has been based largely on the toxicity values reported for dogs.

During a literature review on N-hydroxylation of aromatic amines, one of us (HPP) read that an experiment with para-aminopropiophenone (PAPP) in dogs was discontinued because it was highly toxic by intravenous injection, but the dose was not stated (JAGOW et al. 1966). A subsequent review of the literature showed that PAPP's toxicity varied between species and even strains. For instance, DURIE and DOULL (1968) reported intraperitoneal PAPP LD50's of 273 and 85 mg/kg in Holtzman and Charles River rats, respectively. The intraperitoneal LD50 of PAPP in mice is given by LANPHIER et al. (1947) as 223 mg/kg and by FITZGERALD et al. (1974) as 86 mg/kg. The intravenous LD50 of the hydrochloride salt of PAPP to dogs was reported to be 7.2 mg/kg (ROSE et al. 1947), and three of five dogs died when orally administered 50 mg/kg PAPP (VANDENBELT et al. 1944). Although the above data are only preliminary they do suggest that PAPP is highly toxic to canines as compared with rodents. Therefore, acute oral toxicity tests were initiated with coyotes and 14 other species of mammals and birds to determine if PAPP displayed selective toxicity.

MATERIALS AND METHODS

Male albino rats and mice from Simonsen Laboratories, Gilroy, California, were maintained under laboratory conditions 7 to 14 days before testing. Coturnix quail were bred and raised in the laboratory. All the other animals were maintained 7 to 30 days before testing. Food and water were available at all times.

0007-4861/83/0030-0122 $01.00

Except for the male rats, mice, and red-winged blackbirds, sexes of all the other animals were mixed. The coturnix quail, starlings, red-winged blackbirds, black-billed magpies, and crows were fasted 4 to 5 hours before dosing but none of the other animals were fasted. PAPP (Eastman Kodak Company) was prepared in either cod liver oil, 0.05% Carbopol 914, or propylene glycol. In the above-mentioned birds doses of PAPP were introduced orally directly into the stomach via syringe with attached polyethylene tubing. In rats and mice PAPP was introduced into the stomach with syringe and intubation needle. For the remaining animals PAPP was administered by syringe to the back of the mouth and it was swallowed. After dosing, animals were observed periodically during the first few hours and the posttreatment observation period was 7 days. The acute oral LD50 with 95% confidence limits was calculated by the methods of THOMPSON (1947) and THOMPSON and WEIL (1952).

RESULTS AND DISCUSSION

Of the 15 species of mammals and birds tested only the coyote, cat, bobcat, and kit fox were considered to be highly susceptible to the toxic effects of orally administered PAPP (Table I). These four species represent two families, the Canidae and the Felidae. As compared to domestic dogs, coyotes are apparently much more sensitive to PAPP. VANDENBELT et al. (1944) reported that dogs survived oral doses of 10 mg/kg and there was 60% survival of dogs dosed at 50 mg/kg. The LD50 of 5.6 mg/kg in coyotes is very low but it probably has no practical value for selectivity as compared with some of the other species. For instance, the theoretical total dose of 56 mg to kill 50% of the average size (10 kg) coyotes would also kill the average size cat, bobcat, and kit fox.

Vomiting was sometimes a complicating factor which probably decreased the toxicity of PAPP in some animals. Except for the badger which vomited at 25 mg/kg and one magpie that vomited at 100 mg/kg, vomiting, if it occurred, was at doses of 100 mg/kg or greater in the other animals. The cat and kit fox exhibited some salivation but no vomiting. Although none of the 12 coyotes used in calculation of the LD50 vomited, 1 of 4 coyotes vomited and survived when orally administered 10 mg/kg PAPP prepared in 0.05% Carbopol 914. The other three coyotes died. Vomiting produced in coyotes by PAPP appears to be dependent upon mode of administration. When PAPP was formulated in cod liver oil or Carbopol and gavaged, the incidence of vomiting was 0% ($n = 12$) and 25% ($n = 4$), respectively. In contrast to the gavaged data, PAPP administered in beef tallow baits to coyotes at a dose of 150 mg has produced 80% vomiting ($n = 5$) and only three died. We cannot explain the low incidence of vomiting in gavaged coyotes and the high incidence in coyotes receiving tallow baits. However, it may be due to the ferrihemoglobin concentration. PAPP induced vomiting in dogs when the ferrihemoglobin concentration ranged from 61-80%, but no vomiting was observed in six dogs when the concentration ranged from 81-90% (BODANSKY and GUTMANN 1947).

TABLE I. Acute oral toxicity of p-aminopropiophenone (PAPP) to animals.

Animal (Scientific name)	Weight range (kg)	No. animals per No. dose levels tested[1]	Vehicle	LD50 (mg/kg) with 95% confidence limits or Remarks[2]
Coyote (Canis latrans)	8.2-12.7	4 X 3	Cod liver oil	5.6 (3.0-10.4)
Striped skunk (Mephitus mephitus)	1.4-3.6	2 X 3	0.05% Carbopol 914	>400; 1/1 vomited but died at 800
Raccoon (Procyon lotor)	1.8-3.6	2 X 2	"	142 (-)[3]
Badger (Taxidea taxus)	4.5-6.8	2 X 2	"	0/2 deaths at 50; 1/2 deaths at 100; 1/1 vomited at 25; 1/2 vomited at 50; survivor vomited at 100
Cat (Felis libyca domestica)	1.8-4.1	3 X 3	"	5.6 (3.5-8.9)
Bobcat (Lynx rufus)	3.7-8.7	2 X 3	"	10 (5-20)
Kit fox (Vulpes velox)	1.6-2.3	2 X 3	"	14.1 (-)
Golden eagle (Aquila chrysaetos)	4.4-5.3	1 X 4	"	1/1 survived at 50, 100, 200, 400. Vomiting at 200 and 400.
Rat (Rattus norvegicus, albino)	0.3-0.38	6 X 3	Propylene glycol	177 (119-262)

TABLE I. Continued.

Animal (Scientific name)	Weight range (kg)	No. animals per No. dose levels tested[1]	Vehicle	LD50 (mg/kg) with 95% confidence limits or Remarks[2]
Mouse (Mus musculus, albino)	0.031-0.042	10 X 3	"	233 (186-292)
Coturnix quail (Coturnix coturnix)	0.1-0.12	2 X 2	"	>316
Starling (Sturnus vulgaris)	0.068-0.087	2 X 2	"	>316; 2/2 vomited at 100 and 316.
Red-winged blackbird (Agelaius phoeniceus)	0.059-0.075	2 X 3	"	133 (-)
Black-billed magpie (Pica pica)	0.13-0.17	2 X 3	"	178 (100-316); 1/2 vomited at 100; 2/2 vomited at 316.
Common crow (Corvus brachyrhynchos)	0.29-0.39	--	"	1/1 deaths and vomiting at 316, 562, and 1000; 1/2 deaths and vomiting at 178.

[1] As for example with the coyotes: 4 coyotes each were tested per each of 3 dose levels; therefore 12 coyotes were used.

[2] Only those animals that vomited are so designated.

[3] Confidence limits could not be determined.

Vomiting induced by PAPP must be controlled before PAPP can be effectively used in predator management control. Tests are planned with PAPP baits containing antiemetics to prevent or delay emesis so that a lethal dose is absorbed.

It has been determined for rats and mice that PAPP is a potent indirect oxidant of hemoglobin to ferrihemoglobin and *in vivo* formation of ferrihemoglobin after oral administration in dogs was first shown by VANDENBELT et al. (1944). Ferrihemoglobin is not produced after *in vitro* PAPP application but it is after *in vivo* administration and it has been shown in dogs that PAPP is metabolized to para-hydroxylaminopropiophenone which is responsible for converting hemoglobin to ferrihemoglobin (GRAFFE et al. 1964). Although it has not been demonstrated biochemically, it is plausible that the difference between susceptible and nonsusceptible animals in the present study is the metabolic pathway responsible for N-hydroxylation of PAPP.

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Accepted November 1, 1982