TOXICOLOGY AND APPLIED PHARMACOLOGY 26, 532–538 (1973)

A Summary of the Acute Toxicity of 4-Aminopyridine to Birds and Mammals

EDWARD W. SCHAFER, JR., RONALD B. BRUNTON AND DONALD J. CUNNINGHAM

U.S. Bureau of Sport Fisheries and Wildlife, Wildlife Research Center, Denver, Colorado 80225

Received January 9, 1973; accepted May 10, 1973

A summary of the Acute Toxicity of 4-Aminopyridine to Birds and Mammals. SCHAFER, E. W., JR., BRUNTON, R. B. AND CUNNINGHAM, D. J. (1973). *Toxicol. Appl. Pharmacol.* **26**, 532–538. Acute toxicity data for 41 species of birds and mammals are summarized for 4-aminopyridine (4AP), an agent that can be used to control damage caused by birds. Acute po LD50 values for the free base of 4AP ranged from <1.0 mg/kg for the shiny cowbird (*Molothrus bonariensis*) to 20 mg/kg for the laboratory rat (*Rattus norvegicus*). Birds and mammals appear equally sensitive to 4AP intoxication, and po LD50 values were generally less than 10 mg/kg.

4-Aminopyridine (4AP) is an acutely toxic substituted pyridine. In mammals, it produces the following sequence of clinical signs: hyperexcitability, salivation, tremors, muscular incoordination, clonic and tonic convulsions, cardiac or respiratory arrest, and death (von Haxthausen, 1955; Fastier and McDowall, 1958; Vohra *et al.*, 1965; Lemeignan and Lechat, 1967; Lechat *et al.*, 1968). At doses near the LD50, initial effects are usually noted in 10–15 min and death often occurs 15 min to 4 hr later. Occasionally, the tremor and/or convulsive stages are accompanied by audible vocalizations produced by strong, involuntary contractions of the diaphragm (Sobek *et al.*, 1968).

Goodhue *et al.* (1964) found that 4AP intoxication evoked pronounced behavioral responses in many gregarious avian species. Birds ingesting 4AP became disoriented and emitted distress calls that caused other, nonintoxicated birds to leave the area. This frightening effect has subsequently been used to reduce damage caused by urban and rural populations of many species of birds (Flynn, 1965; Goodhue and Baumgartner, 1965a,b, 1967; Guarino and Schafer, 1967; West *et al.*, 1967; Woronecki *et al.*, 1967; De Grazio *et al.*, 1971, 1972). In frightening birds with 4AP, only minute amounts of chemical were used, and very few birds were killed.

In this paper all acute toxicity data for 4AP on mammals and birds of which we were aware have been assembled. About half the entries in Table 1 represent unpublished data gathered at our laboratory; the rest were taken from the literature or furnished by personal communication.

TABLE 1

ACUTE TOXICITY OF 4-AMINOPYRIDINE TO 41 ANIMAL SPECIES

Species (mixed or unknown sex unless noted)	Route[a]	Carrier	LD50 (mg/kg)	95% confidence limits (mg/kg)	Source of data
MAMMALS					
White rat (*Rattus norvegicus*)	po	Water	32–32.5 (HCl)[b]	—	Goodhue and Baumgartner (1965a,b, 1967)
	po	Water	28 (HCl)	—	Deichman and Gerarde (1969)
	po	Water	20	—	Goodhue, personal communication
	ip	Water	6.50	5.60–7.55	DWRC[c]
White mouse (*Mus musculus*)	ip	Water	14.7	13.9–15.5	Humphreys (1962)
	ip	Water	10	—	Vohra *et al.* (1965)
	ip	Water	9	—	Fastier and McDowall (1958)
	sc	Water	5	—	von Haxthausen (1955)
	iv	Water	7	—	Lemeignan and Lechat (1967)
	ic	Water	10–20 μg/animal	—	Fastier and McDowall (1958)
Hog (*Sus scrofa*)	po	Grain	17.8 (HCl)	—	Goodhue and Baumgartner (1965a,b, 1967)
Dog (*Canis familiaris*)	po	Grain	11.9 (HCl)	—	Goodhue and Baumgartner (1965a,b, 1967)
	po	Capsule	4.0	—	Deichman and Gerarde (1969)
	po	Water	3.7	—	Goodhue, personal communication
	im	Water	3.5	—	Shaw and Bentley (1952, 1955)
Rabbit (*Oryctolagus cuniculus*)	dm	Water	327	—	Deichman and Gerarde (1969)
BIRDS					
Mallard (*Anas platyrhynchos*)	po	Propylene glycol	4.2	—	Schafer (1972)
Sparrow hawk (*Falco sparverius*)	po	Propylene glycol	5.6	4.2–7.5	DWRC
Domestic chicken (*Gallus gallus*)	po	Water	35 (HCl)	—	Goodhue, personal communication
(2–3 wk)	po	Water	15 (HCl)	—	Deichman and Gerarde (1969)

TABLE 1—*continued*

Species (mixed or unknown sex unless noted)	Route[a]	Carrier	LD50 (mg/kg)	95% confidence limits (mg/kg)	Source of data
Bobwhite (*Colinus virginianus*)	po	Water	15 (HCl)	—	Goodhue, personal communication
Coturnix quail (*Coturnix coturnix*).♂	po	Propylene glycol	7.65	6.59–8.89	DWRC
♀	po	Propylene glycol	8.05	7.01–9.24	DWRC
Ring-necked pheasant (*Phasianus colchicus*):♀	po	Propylene glycol	7.5	5.7–9.8	Schafer (1972)
(4 wk)	po	Propylene glycol	5.6	3.2–10	DWRC
Ring-billed gull (*Larus delawarensis*)	po	Water	8 (HCl)	—	Goodhue, personal communication
Common pigeon (*Columba livia*)	po	Water	20 (HCl)	—	Goodhue, personal communication
	po	Propylene glycol	7.5	—	DWRC
Mourning dove (*Zenaidura macroura*)	po	Propylene glycol	8.1	7.5–10	Schafer (1972)
Ruddy ground dove (*Columbigallina talpacoti*)	po	Grain	<25	—	DWRC
Scaled dove (*Scardafella squammata*)	po	Grain	>4	—	DWRC
White-winged dove (*Zenaida asiatica*)	po	Propylene glycol	13	—	Schafer (1972)
Brown-throated parakeet (*Aratinga pertinax*)	po	Grain	≅10	—	DWRC
Budgerigar (*Melopsittacus undulatus*)	po	Propylene glycol	5.6	—	DWRC

Orange-fronted parakeet (*Aratinga canicularis*)	po	Grain	≅12	—	DWRC
Robin (*Turdus migratorius*)	po	Propylene glycol	4.2	2.4–7.5	DWRC
Starling (*Sturnus vulgaris*)	po	Water	14 (HCl)	—	Goodhue and Baumgartner (1965a)
	po	Pellet	<6	—	DWRC
	po	Propylene glycol	4.9	3.6–6.6	Schafer (1972)
Black-billed magpie (*Pica pica*)	po	Propylene glycol	2.4	—	DWRC
Common crow (*Corvus brachyrhynchos*)	po	Propylene glycol	2.4	—	Schafer (1972)
Green jay (*Cyanocorax yncas*)	po	Propylene glycol	<10	—	DWRC
Yellow-billed magpie (*Pica nuttalli*)	po	Propylene glycol	2.4	—	DWRC
Boat-tailed grackle (*Cassidix mexicanus*)	po	Propylene glycol	3.2	1.8–5.6	Schafer (1972)
	po	Water	1.7–7.1	—	DWRC
Brown-headed cowbird (*Molothrus ater*)	po	Propylene glycol	4.2	—	Schafer (1972)
Bronzed cowbird (*Tangavius aeneus*)	po	Propylene glycol	3.2	1.8–5.6	Schafer (1972)
Common grackle (*Quiscalus quiscula*)	po	Propylene glycol	2.4	—	DWRC
Red-winged blackbird (*Agelaius phoeniceus*).♂	po	Water	8.5	—	DWRC
	po	Water	3.2 (HCl)	—	DWRC
	po	Propylene glycol	2.4	1.5–3.8	Schafer (1972)
	im	Propylene glycol	2.4	—	DWRC
Shiny cowbird (*Molothrus bonariensis*)	po	Propylene glycol	<1.0	—	DWRC
Tricolored blackbird (*Agelaius tricolor*)	po	Propylene glycol	4.2	—	DWRC

TABLE 1—*continued*

Species (mixed or unknown sex unless noted)	Route[a]	Carrier	LD50 (mg/kg)	95% confidence limits (mg/kg)	Source of data
Blue-black grassquit (*Volatina jacarina*)	po	Grain	10	5.6–18	DWRC
Dickcissel (*Spiza americana*)	po	Grain	≅10	—	DWRC
House finch (*Carpodacus mexicanus*)	po	Propylene glycol	5.6	—	DWRC
Golden-crowned sparrow (*Zonotrichia atricapilla*)	po	Propylene glycol	5.6	3.2–10	DWRC
House sparrow (*Passer domesticus*)	po	Propylene glycol	7.5	—	DWRC
	po	Water	4.0	—	Schafer (1972)
	po	Water	3.8	—	DWRC
	po	Water	3.6	—	Goodhue and Baumgartner (1965a)
	dm	Acetone	>100	—	DWRC
Red-billed quelea (*Quelea quelea*)	po	Propylene glycol	5.6	3.2–10	DWRC
	dm	Acetone	>100	—	DWRC
Ruddy-breasted seedeater (*Sporophila minuta*)	po	Grain	<7.2	—	DWRC
White-crowned sparrow (*Zonotrichia leucophrys*)	po	Propylene glycol	5.6	3.2–10	Schafer (1972)

[a] po = per os, ic = intracerebral, im = intramuscular, ip = intraperitoneal, iv = intravenous, sc = subcutaneous, dm = dermal.
[b] HCl = Hydrochloride salt.
[c] Denver Wildlife Research Center.

METHODS

Previously unpublished data from the Denver Wildlife Research Center (DWRC) were derived primarily by the po methods described by DeCino *et al.* (1966), Schafer (1972), and Schafer *et al.* (1967). Other methods of oral administration included force-feeding synthetic pellets (Pan and Caslick, 1966) or treated grain. Dermal toxicity was determined by the method described by Schafer *et al.* (1969). All test animals were adults unless noted in the table. LD50 values and 95% confidence limits were derived by the moving-point interpolation method described by Thompson (1948), Thompson and Weil (1952), and Weil (1952). The 4AP used was technical material of about 95% purity.

Methodology for other data can be found in the cited articles.

RESULTS

A summary of acute toxicity data is presented in Table 1. The data indicate that 4AP is highly toxic to all 41 animal species tested. Although the LD50 values varied widely among species, most were below 10 mg/kg. The hydrochloride salt was somewhat less toxic than the free base, but the difference was less than a factor of 3.

Among the mammals, dogs were the most sensitive to intoxication with 4AP (po LD50 = 3.7 mg/kg), and rats were the least sensitive (po LD50 = 20 mg/kg). Mice and hogs appeared to be intermediate in susceptibility, although the modes of administration were not comparable.

Birds were approximately as sensitive to 4AP intoxication as mammals and showed no obvious differences in sensitivity between species or genera when variables such as carriers and chemical form (base or HCl) were disregarded. The shiny cowbird was the most sensitive bird (po LD50 <1.0 mg/kg), and the chicken apparently the least sensitive (po LD50 = 15–35 mg/kg); however, the chicken values were for 4AP HCl. Game species such as mallards, bobwhites, pheasants, and various doves were intermediate.

In our tests, birds showed the same signs of 4AP intoxication as mammals. In addition, birds of three orders (Psittaciformes, Galliformes, and Passeriformes) displayed the very prominent audible vocalizations that make 4AP useful as a frightening agent to control damage caused by birds.

REFERENCES

DeCino, T. J., Cunningham, D. J. and Schafer, E. W., Jr. (1966). Toxicity of DRC-1339 to starlings. *J. Wildl. Manag.* **30**, 249–253.

De Grazio, J. W., Besser, J. F., DeCino, T. J., Guarino, J. L. and Starr, R. I. (1971). Protecting ripening corn from blackbirds with 4-aminopyridine. *J. Wildl. Manag.* **35**, 565–69.

De Grazio, J. W., Besser, J. F., DeCino, T. J., Guarino, J. L. and Schafer, E. W. (1972). Protecting ripening corn from blackbirds by broadcasting 4-aminopyridine baits. *J. Wildl. Manag.* **36**, 1316–1320.

Deichman, W. B. and Gerarde, H. W. (1969). *Toxicology of Drugs and Chemicals*, p. 93. Academic Press, New York.

Fastier, F. N. and McDowall, M. A. (1958). A comparison of the pharmacological properties of three isomeric aminopyridines. *Aust. J. Exp. Biol. Med. Sci.* **36**, 365–372.

FLYNN, R. G. (1965). New techniques for reducing bird strikes at airports. Presented at the Aircraft Design and Technology, Nov. 16–18. American Institute of Aeronautics and Astronautics, 65–748, 18 pp. (Abstract.)

GOODHUE, L. D. AND BAUMGARTNER, F. M. (1965a). Applications of new bird control chemicals. *J. Wildl. Manag.* **29**, 830–837.

GOODHUE, L. D. AND BAUMGARTNER, F. M. (1965b). The Avitrol method of bird control. *Pest Control* **33**, 16–17, 46–48.

GOODHUE, L. D. AND BAUMGARTNER, F. M. (1967). Pest bird control. *Soap Chem. Spec.* **43**, 56–60.

GOODHUE, L. D., REINERT, A. J. AND WILLIAMS, R. D. (1964). Amino substituted heterocyclic nitrogen compounds as bird and rodent repellents. *U.S. Pat.* 3,150,041. 6 pp.

GUARINO, J. L. AND SCHAFER, E. W. (1967). Magpie reduction in an urban roost. *U.S. Fish Wildl. Serv. Spec. Sci. Rep. Wildl.* **104**, 5 pp.

HUMPHREYS, S. R. (1962). Toxicity and antileukemic effectiveness of pyridine derivatives and 1,2,4-thiadiazol derivatives in mice—relation to nicotinamide antagonism. *Cancer Res.*, Suppl. 22, Part 2, 483–550.

LECHAT, P., DEYSSON, G., LEMEIGNAN, M. AND ADOLPHE, M. (1968). Comparison of the acute toxicity of some aminopyridines in vivo (in mice) and in vitro (on cell cultures). *Ann. Pharm. Fr.* **26**, 345–349.

LEMEIGNAN, M. AND LECHAT, P. (1967). Anticurare action of aminopyridines. *C.R. Acad. Sci. Ser. D* **264**, 169–172.

PAN, H. P. AND CASLICK, J. W. (1966). Rapid dosing of food pellets in toxicological studies with birds. *Avian Dis.* **10**, 375–377.

SCHAFER, E. W. (1972). The acute oral toxicity of 369 pharmaceutical, pesticidal and other compounds to wild birds. *Toxicol. Appl. Pharmacol.* **22**, 315–330.

SCHAFER, E. W., STARR, R. I., CUNNINGHAM, D. J. AND DECINO, T. J. (1967). Substituted phenyl *N*-methylcarbamates as temporary immobilizing agents for birds. *J. Agr. Food Chem.* **15**, 287–289.

SCHAFER, E. W., WEST, R. R. AND CUNNINGHAM, D. J. (1969). New starling toxicant: DRC-1347. *Pest Control* **37**, 22–24, 30.

SHAW, F. H. AND BENTLEY, G. A. (1952). Morphine antagonism. *Nature (London)* **169**, 712–713.

SHAW, F. H. AND BENTLEY, G. A. (1955). Morphine antagonism. *Aust. J. Exp. Biol.* **33**, 143–152.

SOBEK, V., LEMEIGNAN, M., STREICHENBERGER, G., BENOIST, J. M., GOGUEL, A. AND LECHAT, P. (1968). Antagonism between curarizing agents and aminopyridines as studied in the isolated rat diaphragm. *Arch. Int. Pharmacodyn. Ther.* **171**, 356–368.

THOMPSON, W. R. (1948). Use of moving averages and interpolation to estimate median-effective dose. I. Fundamental formulas, estimation of error and relation to other methods. *Bacteriol. Rev.* **11**, 115–145.

THOMPSON, W. R. AND WEIL, C. S. (1952). On the construction of tables for moving average interpolation. *Biometrics* **8**, 51–54.

VOHRA, M. M., PRADHAN, S. N., JAIN, P. C., CHATTERLEE, S. K. AND ANAND, N. (1965). Synthesis and structure-activity relations of some aminopyridines—Imidazo pyridines and triazole pyridines. *J. Med. Chem.* **8**, 296–304.

VON HAXTHAUSEN, E. (1955). Aminopyridine and its derivatives. *Arch. Exp. Pathol. Pharmakol.* **226**, 163–171.

WEIL, C. S. (1952). Tables for convenient calculation of median effective dose (LD_{50} or ED_{50}) and instructions in their use. *Biometrics* **8**, 249–263.

WEST, R. R., BESSER, J. F. AND DE GRAZIO, J. W. (1967). Starling control in livestock feeding areas. *Proc. 3rd Vert. Pest Control Conf.* pp. 89–93.

WORONECKI, P. P., GUARINO, J. L. AND DE GRAZIO, J. W. (1967). Blackbird damage control with chemical frightening agents. *Proc. 3rd Vet. Pest Control Conf.* pp. 54–56.