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TOXICITY OF HALOGENATED OXYQUINOLINES IN DOGS. A CLINICAL STUDY

II. HISTORY, SYMPTOMS, LABORATORY FINDINGS, THERAPY, AND FOLLOW-UP*

By

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LANNEK, BIRGITTA: *Toxicity of halogenated oxyquinolines in dogs. A clinical study. II. History, symptoms, laboratory findings, therapy, and follow-up.* Acta vet. scand. 1974, *15*, 219—238. — Intoxication due to short-term oxyquinoline therapy was studied in 100 dogs, which had been so treated because of diarrhoea (except in 2 cases). The latter condition was in itself mild and uncomplicated. The main symptoms of intoxication were listlessness or excitation and nervousness, aggressiveness, tremor, convulsions, and salivation. Clinical examination revealed myocarditis and liver injury. Mortality, i.e. the sum of spontaneous deaths and euthanasia, amounted to 30 %. The treatment considered to be most important was sedation and anticonvulsant measures. It was further essential to correct the dehydration, which was often present. A follow-up investigation showed that approx. ⅓ of the dogs which had recovered from the acute intoxication developed recurrent convulsions within the next 3 years.

aggressiveness; convulsions; dehydration; epileptic seizures; excitation; listlessness; liver injury; myocardial injury; nervousness; oxyquinolines.

Toxic effects of the administration of oxyquinolines in dogs have been reported (*Schantz & Wikström* 1965, *Hangartner* 1965, *Müller* 1967, *Püschner & Fankhauser* 1969, *Lannek* 1973). The treatment was in most cases given because the dogs had diarrhoea. The symptoms appeared after a few hours or a day. CNS disturbances, varying from excitation, slight ataxia, and muscle

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tremor to convulsions, intermittent or more continuous, and involving large muscle groups, were noted. In some cases a comatose condition developed, now and then interrupted by convulsions. Severely affected dogs showed a picture of shock.

Post-mortem examination revealed myocarditis or fatty infiltration of the myocardium, liver degeneration (*Schantz & Wikström*), encephalomalacia, myocardosis, hepatosis, and nephrosis or nephritis (*Hangartner*), hyperaemia in the brain and leptomeninges and haemorrhages in kidneys and brain (*Müller*), and ischaemic processes in the brain (*Püschner & Fankhauser*). An analysis of 100 cases (*Lannek* 1973) showed that old dogs fell ill more often than expected from the distribution of age classes in a population of clinical inpatients and of licensed dogs.

MATERIAL AND METHODS

The clinical cases have been presented previously (*Lannek* 1973). Analyses of blood, urine, and cerebrospinal fluid and of the chemical composition of blood plasma or serum were made at the Department of Clinical Biochemistry (*Åberg & Crabo* 1965). Collection of cerebrospinal fluid (*Wikström* 1969), recording of electrocardiograms (*Lannek* 1949) and liver biopsy technique (*Lannek* 1968) have been described. Histological preparations and examination of liver-biopsy specimens were made at the Department of Pathology and, in 1 case, at the State Veterinary Medical Institute.

Sick dogs admitted to the clinic were under observation until they were sent home or died or were killed. Collection of specimens and recordings were repeated at intervals. Some of these thus represent the newly arrived dog, which had not yet been subjected to any therapy at the clinic, whereas others represent later phases, when different kinds of treatment had been given. Some therapeutic measures, like fluid infusions, may have interfered with the clinical picture, which is per se characteristic for oxyquinoline intoxication. The account of laboratory findings (see the tables) will mainly include observations from an early phase of the disease. It was not always possible to obtain specimens at the most appropriate time, however. In many cases blood sampling failed because of a highly viscous, tar-like consistency of the blood, and biopsy specimens of the liver could not be obtained because of frequent fits.

History

In nearly all the cases (98/100) the dogs had been treated for diarrhoea with an oxyquinoline preparation. This condition lasted from a few hours to 3 weeks (*Lannek* 1973, Table 1). Vomiting occurred only rarely. A constant observation was that the general condition of the dogs did not seem to be affected by their enteritis. Thus, in most cases, the appetite was normal and the dogs showed a lively behaviour, until the symptoms of oxyquinoline poisoning set in. With a few exceptions, the owners found no reason to consult a veterinarian for examination and treatment of the primary diarrhoea. In most cases, an oxyquinoline preparation seems to have been given, because the owner knew by experience that such drugs were useful in the treatment of mild enteritic disturbances. In Sweden they were available without a prescription until June 1972.

One dog received oxyquinoline tablets, which the owner gave by mistake, instead of an anthelmintic. Another dog was given such tablets by the family's 2-year-old son. These 2 dogs had no diarrhoea.

The majority of cases (66/100) had been treated for only a day or less before the alarming symptoms of intoxication appeared. In the rest, the treatment had continued for 2—4 days. (Information was lacking in 2 cases). When the originally mild disease was thus suddenly aggravated and complicated, the medical treatment was stopped, except in 2 dogs (cases nos. 72 and 98).

The daily dose varied greatly, or between 6.9 mg and 250 mg per kg.

In 59 cases, symptoms were observed within 12 hrs. after the last administration of tablets. The shortest interval was less than ½ hr. and the longest was 48 hrs. In 4 cases the interval between dosage and onset of disease could not be confirmed.

Symptoms

The first symptoms which were observed by the owner were changes in temperament, such as listlessness or nervousness, restlessness, aggressiveness, difficulties to rise, ataxia, a stiff gait, and, later, salivation and convulsions. Most of the dogs had an anxious look and seemed to be disoriented. Approximately half the dogs were brought to the clinic as emergency cases.

The symptoms seen at the clinic varied greatly in intensity. In a few cases the symptoms observed and reported by the owner did not reappear while the dog was at the clinic. Some other dogs showed only slight muscle tremor or single convulsions alternating with listlessness or nervousness and hyperactivity; the latter 2 conditions were present in nearly all the cases. Many dogs, but not the majority, became aggressive. This was sometimes so marked, that it was difficult to handle and examine the dog. In more severely affected cases convulsions (Fig. 1) recurred at short intervals. One dog (case no. 68), for instance, ruptured both Achilles' tendons while tied on a table for infusion therapy. Rigidity was marked between the seizures (Fig. 2) and many dogs could not rise or walk without great difficulties. Salivation was in most cases profuse with production of low-viscous saliva (Figs. 3, 4). It also occurred in dogs that had no convulsions. Pools of saliva would be found on the floor round the dog after ½ hr. Hypersensitivity developed occasionally, and convulsions could be elicited by a sudden noise or by the pain from application of electrocardiograph clips. Yawling was often noted. Observable reflexes, as pupil, corneal, flexor (toe pinch), extensor thrust, and knee jerk reflexes, were not disturbed, but convulsions were often provoked when the reflexes were examined. Tachycardia and tachypnoea were regularly seen during the convulsions, and body temperature could then rise to 41°C. Visible mucous membranes were red to dark red. Increased skin turgidity and dry appearance of the conjunctival membranes gave the impression of dehydration. Some dogs were in a state of shock or coma, when they were presented. Mucous membranes were whitish or cyanotic, and the palpable pulse (femoral artery) was rapid and faint. Observable reflexes were absent. The skin was inelastic and leathery, and the coat looked bedraggled. The body temperature was low (less than 37°C) and the extremities were cold and clammy. The eyes were deeply sunken and the cornea was dry. At vein puncture the blood was dark and viscous like tar. It was then difficult to obtain more than a very small blood specimen. Catheterization of the bladder resulted in only a few drops of highly concentrated urine. Such dogs would die within a few hours or a day.

Four of the dogs died within a few minutes after they had been brought to the clinic.

Laboratory findings

Blood values are shown in Table 1 and plasma and serum chemical composition in Table 2. The data of the oxyquinoline group are compared with normal values, as stated by *Paulsson & Åberg* (1965) and *Kirk* (1971). Columns 5 of the tables show some data obtained in dogs suffering from diarrhoea, which were kept as inpatients at the clinic over the corresponding period. These dogs were selected from the clinical records as controls which had diarrhoea but were not treated with oxyquinolines. Their general condition may have been somewhat more affected by the enteric disorder, however, and a greater fraction of them also had vomiting.

The following urine values were determined: Colour, reaction, specific gravity, protein, glucose, cast, and, in some selected cases, bilirubin, urobilin, and haemoglobin. Colour was normal yellow (n = 50). Reaction was alkaline (n = 28), acid (n = 19), or neutral (n = 3). According to the general view, the urine reaction in normal dogs is on the acid side (*Åberg & Crabo, Kirk*). In 100 cases, selected by random and disregarding the diagnosis, kept as inpatients at the clinic during 1965, the reactions were distributed as follows: Alkaline 38, acid 29, and neutral 33. It is the author's experience that the urine reaction is often alkaline or neutral in dogs in which kidney disease or acid-base imbalance is not present. Specific gravity varied between 1.005 and 1.048 (n = 43). According to *Kirk,* the normal range is 1.018—1.060. In 14 cases of the present material it was lower than 1.018. Nine of these had been treated with fluid infusions less than 20 hrs. before the urine specimens were obtained. The remaining 5 dogs were 12, 10, 10, 9, and 1 years old, respectively. It is well known that chronic nephritis with low specific gravity of the urine is common in old dogs. Protein was present in 38 cases (n = 50). The reagent Albustix (tetrabromine phenol blue) was used for small specimens. Strongly alkaline urine gives false-positive reaction with this method.

The results of analysis of cerebrospinal fluid (12 cases) are shown in Table 3. Comparisons are made mainly with normal values (*Crabo & Lannek,* unpublished), because all specimens presented in the first 2 columns were taken by one and the same person and examined at the same laboratory. Strict use of the same technique is of special value in obtaining specimens

Table 1. Blood values of the oxyquinoline group and of control dogs. Probability of identity between columns 1 and 2 is indicated where $P < 0.05$.

	1 Oxyquinoline group	2 Normal values (*Paulsson & Åberg* 1965)	3 P < (cols. 1 and 2)	4 Normal values (*Kirk* 1971)		5 Diarrhoea cases, not treated with oxyquinolines
	m. ± 1 s (number of dogs)	m. ± 1 s (number of dogs)		range	m.	m. ± 1 s (number of dogs)
Erythrocytes (millions/mm³)	6.37 ± 1.12 (82)	6.5 ± 0.97 (25)		5.5 — 8.5	6.8	
Haemoglobin (g/100 ml)	16.12 ± 2.63 (81)	15.5 ± 1.9 (25)		12.0 — 18.0	14.9	
Packed cell volume (ml/100 ml)	49.17 ± 7.73 (87)	48.9 ± 5.1 (25)		37.0 — 55.0	45.5	
Leukocytes/mm³	12.25 ± 4.59 (79)	12.3 ± 2.92 (21)		6 — 18000	11000	
Band neutrophil (%)	1.86 ± 2.54 (81)	1 ± 1.4 (21)	0.025	0 — 3	0.8	3.86 ± 4.00 (14)
Neutrophil „	77.27 ± 11.93 (81)	68 ± 9.9 (21)	0.005	60 — 77	70.0	69.29 ± 12.00 (14)
Lymphocyte „	18.67 ± 8.33 (81)	18 ± 7.7 (21)		12 — 30	20.0	
Monocyte „	0.54 ± 0.81 (81)	6.5 ± 2.8 (21)	0.001	3 — 10	5.2	0.43 ± 0.83 (14)
Eosinophil „	0.83 ± 1.21 (81)	6.5 ± 4.6 (21)	0.001	2 — 10	4.0	1.64 ± 2.97 (14)
Basophil	0	0		rare	rare	

Table 2. Blood-plasma and serum chemical composition (cf. Table 1).

	1 Oxyquinoline group	2 Normal values (*Paulsson & Åberg* 1965)	3 P<	4 Normal values (*Kirk* 1971)	5 Diarrhoea cases, not treated with oxyquinolines
	m. ± 1 s (number of dogs)	m. ± 1 s (number of dogs)		range	m. ± 1 s (number of dogs)
Nonprotein nitrogen 1)	28.89 ± 1.83 (28)	33.1 ± 4.6 (30)	0.001	20 — 36	
Urea nitrogen 1)	20.78 ± 20.69 (58)			10 — 20	
Total protein 2)	7.05 ± 1.12 (41)	7.1 ± 0.7 (28)		5.3— 7.5	
Albumin 2)	4.24 ± 0.85 (32)	4.0 ± 0.7 (28)		3.0— 4.8	
α_1 -globulin 2)	0.33 ± 0.15 (32)	0.34 ± 0.11 (28)			
α_2 - „ 2)	0.34 ± 0.15 (32)	0.35 ± 0.12 (28)			
α_{3-4}- „ 2)	0.38 ± 0.20 (32)	0.35 ± 0.12 (28)		1.3— 3.2	0.29 ± 0.13 (14)
β_1 - „ 2)	0.32 ± 0.23 (32)	0.46 ± 0.36 (28)			
β_{2-3}- „ 2)	0.79 ± 0.24 (32)	1.0 ± 0.47 (28)	0.05		0.74 ± 0.25 (14)
γ - „ 2)	0.67 ± 0.25 (32)	0.70 ± 0.29 (28)			
A/G ratio	1.61 ± 0.56 (32)	1.37 ± 0.42 (28)		1.5— 2.3	
Glucose 1)	85.89 ± 12.50 (26)	70 — 90		60 —100	
Calcium 3)	9.84 ± 12.84 (55)	10.1 ± 1.2 (16)		9 — 11.5	
Inorg. phosphorus 3)	3.82 ± 1.63 (52)	4.7 ± 0.8 (16)	0.005	2.5— 5	
Sodium 4)	148.58 ± 7.20 (79)	147 ± 5.2 (16)		137 —149	154.12 ± 8.29 (17)
Potassium 4)	4.45 ± 0.59 (72)	4.15 ± 0.50 (30)	> 0.01 < 0.02	3.7— 5.8	
Magnesium 4)	1.90 ± 0.60 (15)	1.73 ± 0.25 (10)		1.4— 2.4	
Chloride 4)	110.95 ± 7.25 (81)	113 ± 3.9 (47)	> 0.02 < 0.05	99 —100	
Bicarbonate 5)	20.86 ± 3.79 (71)	22.77 ± 2.23 (21)	> 0.001 < 0.005	18 — 24	
SASAT 6)	68.56 ± 95.15 (76)	17.8 ± 6.2 (166)	< 0.001	< 23 7)	24.83 ± 9.67 (23)
SALAT 6)	52.28 ± 42.34 (75)	20.6 ± 8.4 (143)	< 0.001	< 22 7)	30.91 ± 9.56 (23)
SOCT 8)	5.80 ± 6.17 (53)	2.2 ± 1.6 (159)	< 0.001		2.31 ± 1.31 (20)

1) mg/100 ml blood. 2) g/100 ml serum. 3) mg/100 ml serum. 4) meq./l serum. 5) mmol/l plasma. 6) Karmen units. 7) Sigma Frankel units. 8) Reichard units.

Table 3. Cerebrospinal fluid (m. ± 1 s, or extreme values) of oxyquinoline cases and normal cases.

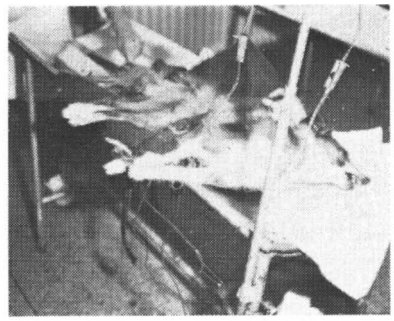
	Oxyquinoline group	Normal (*Crabo & Lannek*)	Normal (*Hoerlein* 1971)
Erythrocytes/mm³	0 —300 (12)[1]	—	—
Leukocytes/mm³	0 —200 (12)[2]	0.83 ± 1.34	1 — 8
Total protein mg/100 ml	14.5 —272.3 (12)[3]	19.99 ± 8.18 (23)	11 — 55
Glucose mg/100 ml	73.3 ± 17.2 (10)[4]	62.04 ± 10.85 (23)	61 — 116
Chloride meq./l	112.78 ± 15.52 (9)[5]	97.1 ± 10.7 (11)	761 — 883 (as NaCl)
Sodium meq./l	146.61 ± 10.76 (9)	142.9 ± 10.2 (13)	—
Potassium meq./l	2.5 — 3.5 (10)	3.44 ± 0.63 (11)	—

[1]: 5 values = 0
[2]: 2 „ = 0
6 „ > 3.5
[3]: 8 „ > 36
[4]: 3 „ > 83
[5]: 5 „ > 117

free from artifacts. It appears that total protein is significantly elevated in 8 cases and that the number of leukocytes is increased in 6 cases, i. e. above mean ± 2 s.

Electrocardiograms were recorded once or several times in 84 cases. Whenever possible, a recording was done soon after the dog had been admitted to the clinic. In 7 cases it was not possible — because of convulsions or hyperactivity — to obtain traces so free from artifacts that they could be analysed. Changes indicating myocardial injury, mainly lowered ST-T, broadened QRS complex, and high peaked T waves, were observed in 34 dogs (Figs. 5, 6, 7, 8). Ventricular extra beats without any other sign of myocardial lesions were seen in 1 case, tachycardia (> 200 beats per min.) in 4, bradycardia (< 70 beats per min.) in 4, and low voltage in 5 cases. Low voltage occurred either in obese dogs or dogs whose fur was diffusely wet from excessive salivation, apparently short-circuiting the electrodes.

Liver-biopsy specimens were taken in 18 dogs. Accumulation of fat droplets in liver cells or in Kupffer cells was present in 15 and circulatory changes (congestion) in 6 dogs. Degenerative or necrotic changes were generally not present in specimens from an early stage but developed in 4 dogs after 3—4 days. A detailed account of the histological findings



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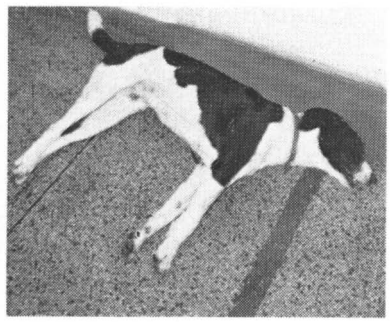

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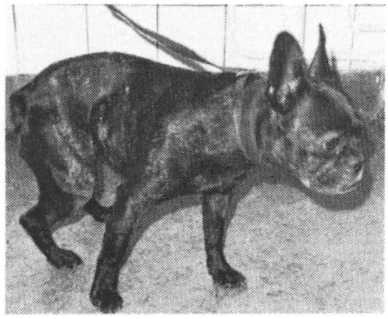

4a

4b

Figure 1. Convulsions in a case of spontaneous poisoning (no. 104, not published) during fluid therapy.

Figure 2. Tetanus-like rigidity of the body between the convulsions in a case of spontaneous vioform poisoning (no. 107, not published).

Figure 3. Spontaneous vioform poisoning (case no. 97) showing salivation, anxious look, and clonic seizures in the mimic muscles.

Figure 4. Spontaneous vioform poisoning (case no. 96). The dog was atactic and fell easily. Note the anxious look and salivation.

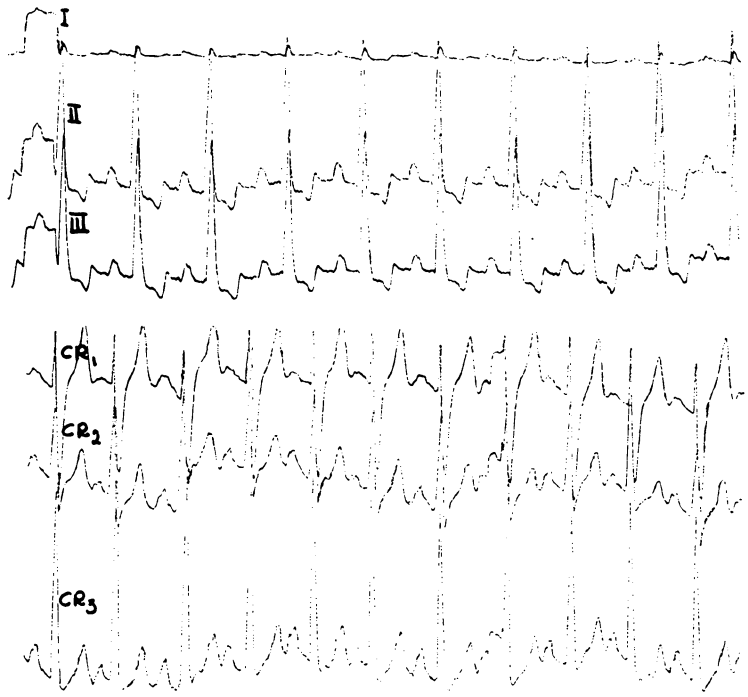

Figure 5. ECG showing depression of the ST segment, broadened QRS, tall peaked T wave and tachycardia (180/min.). Necropsy revealed acute degeneration of the myocardium (case no. 76, Boxer, 6-year-old male. Killed). ($CR_1 = CR_5$; $CR_2 = CR_{6l}$; $CR_3 = CR_{6u}$ (*Lannek* 1949)).

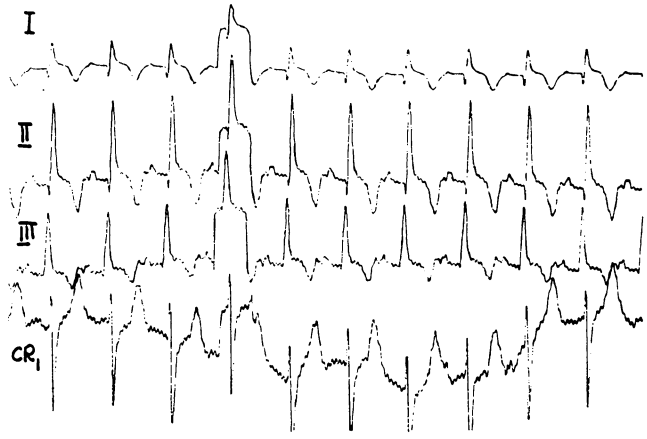

Figure 6. Tachycardia (200/min.), deep negative T_{II}, broadened QRS, high peaked T_{CR_I}, elevated ST junction (case no. 96, French Bulldog, 5-year-old bitch. Recovered).

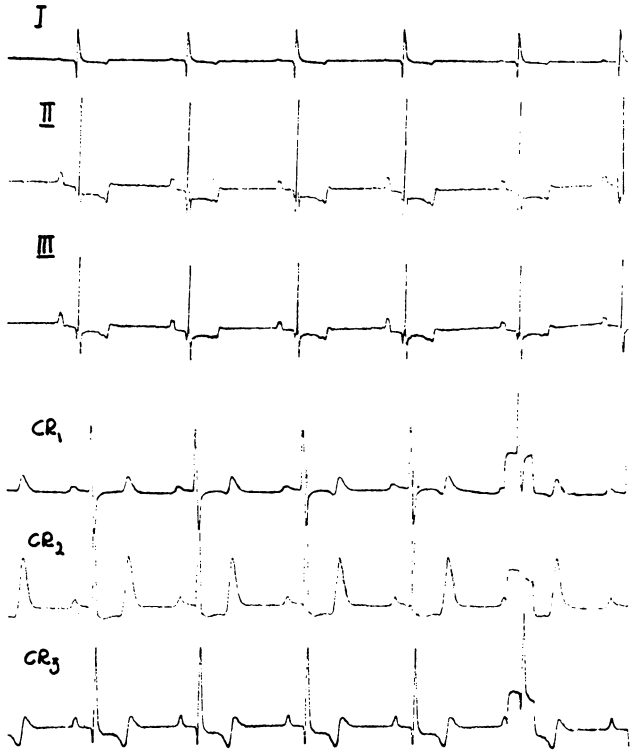

Figure 7. ECG changes in case no. 3 (Miniature Poodle, 10-year-old male. Killed). Note depressed ST segments indicating myocardial injury. Before the recording the dog was treated with phenobarbital because of convulsions.

will be given in association with a description of the post-mortem picture (*Lannek & Jönsson* 1974).

Follow-up

Questionnaires were submitted to the owners of dogs which had been at the clinic because of oxyquinoline poisoning and which had recovered and been discharged up to the spring of 1968. Questions concerned mainly the dog's state of health after returning home. In cases of dogs discharged from the clinic at a later time, the owners were asked the corresponding questions by telephone. This makes altogether 70 questionnaires (30 dogs had died or been killed). Answers were obtained from 54 owners.

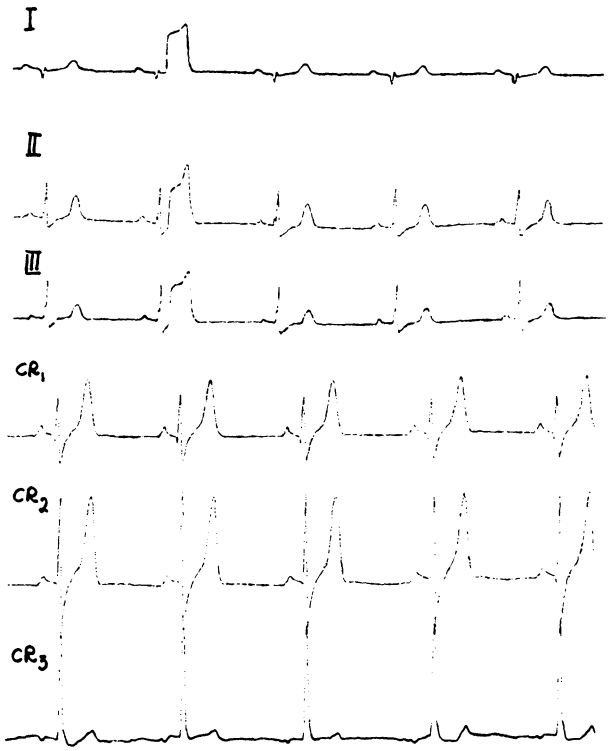

Figure 8. Tall and peaked T waves in leads CR_1 and CR_2, and broadened QRS complexes. Depressed ST in leads II and III (case no. 4, Scottish Terrier, 4-year-old male. Recovered).

Five discharged dogs had been killed because of a later intercurrent disease (tumours in 2 dogs, disc protusion, warfarin poisoning, gonitis, respectively, in the other 3). None of them had shown any symptoms that were referable to the oxyquinoline poisoning.

In 33 dogs no significant symptoms of disease had been noted. In 12 dogs epileptiform seizures of varying severity had developed. This had occurred within 1 month of discharge in 9 and within 1½—3 years in the remaining 3 dogs. As far as is known at the time of writing (the spring of 1973) 6 of these 12 dogs were killed because of epilepsy. Three other dogs had shown consistent nervousness and/or aggressiveness and gun-shyness (1 dog) after they had recovered, and in 1 case the

owner had observed an obvious depression in the mood of the dog. Accordingly, 16, or 32.6 %, of 49 dogs developed CNS disturbances after having passed acute oxyquinoline poisoning.

Forty-nine new questionnaires were sent during the spring of 1973 to owners of dogs which were treated for oxyquinoline poisoning between 1963 and 1969 and were still alive in 1969 and from which answers had been obtained. Thirty-seven answers were received. Twenty-one dogs had died or been killed because of an intercurrent disease (tumours, lameness, heart failure, gastric torsion) or high age. Eight answers represented dogs which had developed CNS disturbances, according to the earlier questionnaire. One of them was now free from symptoms and 2 had improved. Two were still alive but showed recurring convulsions. Three dogs had been killed because of aggravating CNS disturbances.

In 1 dog, which was reported to be free from symptoms in the first questionnaire, convulsions developed later on (5 months after discharge). The dog was killed 4 years later because of leukosis. No CNS disturbances were noted.

Therapy

The primary treatment was sedation of the dog in its often extremely excited condition in order to stop the convulsions. This was done by administration of phenobarbital, usually an initial dose of 1—10 mg per kg body weight. If this was not effective, i. e. if convulsions still occurred, the dog was anaesthetized, usually with a long-acting or short-acting barbiturate. Sedation and anticonvulsive therapy had to be continued for 1 or more days until sufficient clinical improvement was obtained.

Dehydration and suspected hypovolaemic conditions were corrected by intravenous or subcutaneous administration of solutions of glucose (5 %), isotonic sodium-chloride, and Ringer's lactate (Darrow's or Hartmann's solution). Isotonic bicarbonate solution was used in cases of acidosis.

Parenteral nutrition was undertaken whenever the dog did not eat for more than 2 or 3 days. Solutions of isotonic glucose, hypertonic (20 %) fructose, and amino acids were mainly used. Fat emulsions were not infused, because there were often signs of liver lesions. Parenteral nutrition was considered to be necessary only for a few days.

Further therapy was symptomatic and dependent on the dog's daily condition. Myocardial injury complicated by circulatory collapse was treated as congestive heart failure.

DISCUSSION

Poisoning by oxyquinolines for therapeutic use has so far been reported in man and pet animals (dogs and cats). In man, intoxications after long-term administration of large doses have mainly produced lesions in the optical nerve and CNS (*Berggren & Hansson* 1966, *Etheridge Jr. & Stewart* 1966, *Berggren et al.* 1968, *Strandvik & Zetterström* 1968). Amnesia has been reported after short-term administration of oxyquinoline preparations (*Kaeser & Scollo-Lavizzari* 1970, *Kaeser & Wüthrich* 1970, *Kjaersgaard* 1971, *Bengtsson & Vikrot* 1972). Long-term treatment is seldom used in dogs, as the reason for administration is mostly acute diarrhoea. There is convincing evidence that the great majority of dogs do not develop any symptoms of disease after moderate doses, i. e. up to 50 or 100 mg per kg per day, for a few days or a week. There is no doubt, however, that intoxications, even with lethal outcome, may occur after a single dose of a small amount, i. e. 10—20 mg (*Schantz & Wikström* 1965, *Lannek* 1973).

There are few records of experimental feeding moderate to large doses to dogs over a long period of time, but those available indicate that a toxic action can thus be produced (*Griffith* 1969, *Tateishi et al.* 1971). Recently published experiments (*Lannek & Lindberg* 1972 a, b) show that conditions can be induced in which single moderate doses of oxyquinolines will produce an acute and severe disease in dogs. Thus, the presence of fat in the intestine will greatly enhance the absorption of oxyquinoline. Prefeeding with fouled fish will increase the sensitivity of dogs, probably because of a competition in the elimination of oxyquinoline and indol metabolites.

Routine inquiring into the feeding of the dogs that fell ill did not reveal any specific traits or conditions. When a dog becomes ill, it is of course common that the composition of the food is changed in some way. Often small portions of high-quality and tasty food will be offered to the dog. Such food is preferably rich in protein and possibly also in fat. After the promoting effect of fat on absorption of oxyquinolines had been

discovered (*Lannek & Lindberg* 1972 a), special attention was paid to this in the history-taking. It was then confirmed in some cases of oxyquinoline poisoning (not included in the present material) that the oxyquinoline tablets had been given in lumps of Hamburger steak. Samples of the latter were analysed and proved to have a fat content of 18 %. At present, however, one can only speculate on the possibility that selection of special food might play a more general role in the development of the poisoning.

The most obvious symptoms in poisoned dogs are those of increased excitability of the CNS, as hyperactivity, nervousness, tremor, and seizures (grand mal, petit mal, status epilepticus, cf. *Hoerlein* 1971). According to the aetiological classification by *Redding* (1969), they would belong to the group of acquired seizures caused by damage of the brain tissue in metabolic disorders or, in the present cases, chemical intoxication. Several forms of drug toxicity are known to cause neuropathic disorders in man. In no case in the present material did analysis of the CSF show any evidence of bleeding due to puncturing of vessels. The fluid was in all cases excluding 1 (no. 27 in *Lannek* 1973, Table 1) clear and colourless. Nor were there any turbidity or tendency towards coagulation. An increased number of cells was observed in 6 and elevated protein in 8 cases. The deviations were rather slight, however, except in case no. 27. The cells were of lymphoid or mononuclear type. The elevated protein was in 7 cases associated with an increased globulin fraction (1 dog, no. 27, was not examined).

These changes are probably due to toxic substances which have damaged the brain tissue, or caused increased capillary permeability (*Hoerlein*). Other parenchymal lesions are present in the heart and the liver (*Schantz & Wikström, Hangartner*). Electrocardiographic changes indicating myocarditis were observed in at least 34 cases out of 84 in which electrocardiograms were recorded. Changes which, according to *Detweiler* (1968), could be classed as myocardial injury were seen in 34 electrocardiograms. There were depression of the ST segment (Figs. 5, 7, 8), often with the convexity upward (Fig. 7), broadened QRS complex (Figs. 5, 6, 8), negative T wave exceeding 30 % of R wave amplitude in leads II and/or III (Fig. 6), and high peaked T waves (more than 25 % of R wave, Fig. 8). The last mentioned change may indicate left ventricular enlargement

(*Ettinger & Suter* 1970) or may be a non-specific finding. According to *Arbeit et al.* (1960), electrolyte disturbances influence the form and amplitude of the T wave. Characteristically, tall and peaked T waves are seen in hyperpotassaemia (> 5.5 meq./l) and may occur in acidosis in man.

Low QRS amplitudes were probably due to intercurrent non-specific conditions. The finding of diminished QRS amplitudes in all leads is not specific but is frequently encountered in pericardial and/or pleural effusion or other disease conditions resulting in increased mass within the thoracic cavity (*Ettinger & Suter*). According to *Arbeit et al.*, low voltage occurs, for instance, in diffuse myocardial damage and obesity. In the present material, low voltage occurred either in obese dogs or in dogs with excessive salivation.

The heart injury was very likely caused by the oxyquinoline, as there were no history data indicating any heart disease before the dog fell ill. The electrocardiographic picture became gradually normal in dogs that improved generally and recovered. Some dogs had remaining electrocardiographic abnormalities when they were discharged from the clinic. They were re-examined later. In all cases excluding 1 (no. 45) there was complete normalization. In no. 45, the ST-T was still lowered 6 months after discharge. This dog, which had acute oxyquinoline poisoning in 1965, had not shown any symptoms of heart disease as late as in 1973.

Liver injury was revealed by high SOCT, SALAT, and SASAT levels. The heart injury may, to some extent, have contributed to the elevation of SASAT and SALAT. The changes in the liver were confirmed by histological examination of biopsy specimens, which showed fatty infiltration in 15 out of 18 cases. Liver biopsy was not performed in most of the dogs, either because the procedure was considered to be too risky or because the dog was not quiet enough for successful sampling. Like the heart injury, the liver lesions were probably caused by the absorption of oxyquinolines. Except for the laboratory findings, there were no clinical signs or symptoms of liver disease. It is known that the liver has a great reserve capacity, which will conceal even extensive injuries. It has furthermore extraordinary powers of regeneration (cf. *Candlin* 1968). In most cases in which fat infiltration was confirmed in biopsy specimens, a second specimen was taken. Mostly the picture was then normal,

but in some cases necrosis had developed. Experimental oxyquinoline poisoning in dogs (*Lannek & Lindberg* 1974 a) also produces liver injuries (fatty infiltration, elevation of the transaminase levels, and impaired BRS retention). Most of these dogs develop an abnormal electrocardiographic picture as well.

When presented for examination, many of the dogs showed clinical signs of moderate to marked dehydration. The high viscosity of the blood, which not seldom made it impossible to obtain drops of blood at vein puncture, was remarkable. In 20 cases, the PCV value was higher than normal (48 ± 5.1, *Paulsson & Åberg* 1965), but the mean value for 87 cases at admittance was 49.17 ± 7.73. (The median value is 50). Nor were the haemoglobin or total-protein values significantly increased, 16.12 ± 2.63 and 7.05 ± 1.12 g per 100 ml, respectively.

The blood values, collected in Table 1, show that the number of neutrophils is increased, while the eosinophils are decreased as compared with the normal values. This could be signs of an acute alarm reaction.

Table 2 shows the blood-plasma and serum chemical composition. Here are several differences between the oxyquinoline group and the normal values. These differences are statistically significant but small. It may be questioned whether they have a definite biological background. The number of cases in the normal material is in some instances rather low (e. g. for inorganic phosphorus 16, for bicarbonate 21, and for potassium 30 cases).

As regards the serum transaminases SASAT, SALAT and SOCT, the differences between the oxyquinoline group and the normal and diarrhoeic groups are rather great. Dogs suffering from oxyquinoline poisoning have liver injuries. This has been confirmed by histo-pathological examination of liver-biopsy specimens, at necropsy (*Lannek & Jönsson* 1974), and under experimental conditions (*Lannek & Lindberg* 1974 a).

The follow-up investigation shows that many dogs which have successfully recovered from an acute oxyquinoline poisoning develop convulsions. The probability can only be approximately estimated at present, but the figures indicate that it would be at least 30 %. Naturally, the question arises whether convulsions would sometimes be the single observable manifestation of intoxication following oxyquinoline therapy. Epilepsy is common in dogs, and the causes of the brain lesions remain obscure in most cases.

Description of 3 typical cases of oxyquinoline poisoning with varying course

The case number refers to Table 1 in an earlier work (*Lannek* 1973), where the signalment and clinical data are set out.

Case no. 76. The dog, a boxer, 6-year-old male, fell ill after 3 days' treatment with totally 10 tablets (corresponding to 30.4 mg per kg body weight and day) of Fenilor (broxyquinoline). This dog had on several previous occasions been treated with the same drug but never with more than 9 mg per kg and day. The symptoms, which were observed by the owner, were nervousness, excitation, restlessness, and salivation. Some hours later there were frequent muscular twitches of the ears, mouth corners, shoulders, and thighs. On admission to the clinic the next morning, the dog was alternatingly excited and apathetic. It was very atactic and had to lean against the wall or it would fall down. The gait was stiff and the salivation extreme; in the cage were big pools of thin saliva. The dog was dehydrated (PCV 64 %, Hb 20.8 g, and total protein 9.0 g/100 ml) and had tachypnoea, tachycardia, and subnormal temperature (37°C). Now and then there was increased extensor tone in the extremities, or the dog was in opistotonus position. The laboratory tests showed acidosis (bicarbonate 16 mmol/l), slightly increased serum transaminases, diffuse fattening of the liver, and acute myocardial injury (Fig. 5). As the condition successively deteriorated, the dog was killed. Necropsy showed acute non-purulent lymphohistiocytic meningoencephalitis, acute myocardial degeneration, necrosis and fattening of the liver.

Case no. 96. A french bulldog, 5-year-old bitch, had been treated once with Mexaform (clioquinol, vioform), 32.3 mg per kg body weight. About 15 hrs. later the dog began to have „epileptic seizures", which increased in duration and frequency. At the clinic the dog was apathetic, but suddenly she became very excited and had intensive convulsions. Now and then she was very atactic, had profuse salivation (Fig. 4), tachycardia, dyspnoea, and incontinence of urine. In spite of fluid therapy, she was very dehydrated for several days (PCV 60—65 %), and had liver and myocardial injuries (Fig. 6) and slight hyperpotassaemia (5.2 meq./l serum). During the first days after admission the condition deteriorated and she was in very poor health for almost a week. After 12 days on phenobarbital, fluid therapy,

parenteral nutrition, and digitalis glycosides, she was almost free from symptoms and was discharged.

Case no. 88. A miniature poodle, 11-year-old male, was treated for 2 days with Enterovioform (clioquinol, vioform), 102 mg per kg body weight and day. The only symptom observed by the owner and at the clinic was „epileptic seizures", which occurred sporadically. The laboratory findings were normal, and the dog was discharged after a few days of observation and phenobarbital treatment at the clinic.

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SAMMANFATTNING

Toxiciteten av halogenerade oxikinoliner hos hund. En klinisk studie. II. Anamnes, symptombild, laboratorieundersökningar, terapi och uppföljning.

Hundra fall av oxikinolinförgiftning hos hund har studerats. Behandling med oxikinoliner hade (utom i 2 fall) företagits på grund av att hundarna led av en lindrig, okomplicerad diarré. Symptomen utgjordes främst av slöhet eller exitation och nervositet, aggressivitet, muskelryckningar, kramper och salivation. Den kliniska undersökningen avslöjade myokardit och leverskada. Mortaliteten, summan av spontant döda och avlivade fall, var 30 %. Den viktigaste behandlingen är sedativ och antikonvulsiv terapi samt att korrigera den ofta föreliggande dehydreringen. En efterkontroll visar, att ungefär en tredjedel av de hundar som tillfrisknat från det akuta förgiftningstillståndet under de närmast 3 kommande åren får återkommande epileptiska anfall.

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