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TOXICITY OF HALOGENATED OXYQUINOLINES IN DOGS. A CLINICAL STUDY

I. A SURVEY OF CASES*

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LANNEK, BIRGITTA: *Toxicity of halogenated oxyquinolines in dogs. A clinical study. I. A survey of cases.* Acta vet. scand. 1973, *14*, 723—744. — A survey of 100 cases of oxyquinoline poisoning in dogs is presented. The disease, characterized by hyperexcitability of the CNS with convulsions as well as heart and liver injury, runs an acute course. The mortality (euthanized dogs included) was 30 %. Case-history data showed that the oxyquinoline treatment which preceded the disease was given because the dog had incidental diarrhoea. In most cases the drugs were administered for only 1 day before the dog fell ill. The median time from the last dose to onset of symptoms was 12 hrs. Old dogs were affected more often than expected and also showed higher mortality than did young dogs.

convulsions; diarrhoea; dog; halogens; oxyquinolines; poisoning; toxicity.

In 1963—1964 a number of dogs showing convulsions were admitted to the clinic, where the owner's history revealed that a halogenated oxyquinoline derivative had been administered shortly before the dog fell ill. The treatment had been given because the dogs suffered from an uncomplicated diarrhoea. The convulsions, ataxia, salivation, and other symptoms, which will be described in detail (*Lannek*, to be published), could not be explained as complications of mild enteritis. Instead, suspicions accumulated that oxyquinoline treatment may cause a disease

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in dogs, although it was then generally considered that these preparations were virtually free from untoward effects.

A description of 29 cases was published in 1965 (*Schantz & Wikström*). At the same time, *Hangartner* (1965) described 11 cases, 10 in dogs and 1 in a cat, which he considered to be clinical intoxications due to Enterovioform therapy. The symptoms presented in these 2 papers were closely similar.

During the following years, another 71 cases with a similar disease pattern, in which oxyquinolines had been given, were studied at the clinic. The material presented here comprises 100 cases, including those of *Schantz & Wikström*.

After warnings against the use of oxyquinoline preparations to dogs and cats had been published in daily papers and in pharmaceutical and kennel journals in 1966—1967 and later, there was a marked decline in the number of such cases. As from 1969, the disease has been observed sporadically.

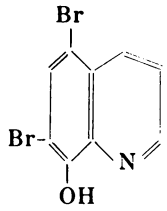
Although there have never been any oxyquinoline preparations recommended for oral use in dogs on the Swedish market, such therapy has no doubt gained great popularity in the treatment of diarrhoeas. In many cases the owner has carried out the therapy on the basis of his experience of such treatment in human beings. Often he was advised to do so by his local veterinarian or by the staff of a pharmacy.

Literature

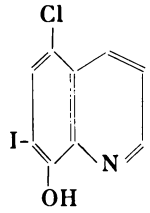
Halogenated oxyquinoline derivatives are a group af antiseptics which have been used, allegedly with successful results, in the treatment of amoebiasis and shigellosis in man (*Gholz & Arons* 1964, *Goodman & Gilman* 1971). Their antimicrobial activity is well documented, but the mode of action is unknown (*Goodman & Gilman*). More recently they have also been used in the treatment of non-specific diarrhoeas and as a preventive measure by travellers liable to alimentary upset. They have been reported to act on bacteria and yeasts.

Some derivatives are also components of solutions, powders, ointments, and other preparations for local treatment of eczema, wounds, burn injuries, and Trichomonas vaginitis.

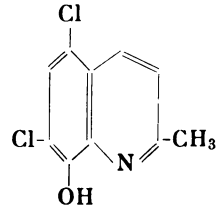
Oxyquinoline derivatives, which have been associated with toxicity manifestations reported in the present paper, are shown below.



Broxyquinoline
(5,7-di-bromo-8-hydroxyquinoline)
Colepur (Draco)
Fenilor (U.C.B.)
Intestopan (Sandoz)



Clioquinol (Vioform)
(5-chloro-7-iodo-8-hydroxyquinoline)
Enterovioform (Ciba)
Entrokinol (ACO)
Mexaform (Ciba)



Chlorquinaldol
(5,7-di-chloro-2-methyl-3-hydroxyquinoline)
Sterosan (Geigy)

Until recently, oxyquinolines were supposed to have a low order of toxicity*. Their marked insolubility was thought to limit their absorption from the intestine, and most of the drugs were said to pass in the faeces (*Goodman & Gilman*). In order to increase the therapeutic efficacy, the active substance of some preparations was in microcrystalline form (Colepur) or was mixed with methyl cellulose (Entrokinol, Colepur), brobenzoxaldin (Intestopan), phanchinon (Mexaform, Zymasan), bismuth (Carbantren), or sapanine as an emulgator (Enterovioform). Our knowledge about their absorption, metabolism, and elimination is incomplete. Although most of an ingested dose will pass without being absorbed, some absorption will no doubt take place. *Palm* (1932) demonstrated that diiodoxyquinoline (5,7-diiodo-8-hydroxyquinoline) given orally was eliminated by the urine as acidic metabolites in rabbits, and *David et al.* (1944) and *Knight & Miller* (1949) found that some absorption always occurred in man after oral administration. The blood levels varied with different preparations. *Haskins & Luttermoser* (1953) found that 5-chloro-7-iodo-8-hydroxyquinoline (vioform) and 5,7-diiodo-8-

* Most of them were withdrawn from the Swedish market in 1972 because of accumulating evidence of toxic side-effects.

hydroxyquinoline (diiodoquin) given orally to rabbits are eliminated as sulphuric and glucuronic acids. They recovered 12—15 % of a 200-mg dose (per kg per day) and 38—50 % of a 20-mg dose in the urine. The ratio of administered and eliminated amounts was presumed to depend upon the solubility of the preparation in the intestine.

Berggren & Hansson (1968) estimated glucuronic-acid conjugates in the urine of man after ingestion of small doses of some oxyquinoline preparations (Enterosept/diiodoxyquinoline/, Fenilor, Enterovioform, and Sterosan). Of Enterovioform 12.5 % and of Sterosan 34.9 % of the dose were eliminated.

Ritter & Jermann (1966) compared the absorption and metabolism of some 8-hydroxyquinolines in rats. They determined free 8-quinolines and their glucuronic-acid and sulphuric-acid derivatives in portal blood, bile, and urine in rats and man. The rate of absorption and excretion in urine and bile was found to follow the same order as the bacteriostatic, fungistatic, and amoebicidal actions of the drugs.

Reports on toxicity in laboratory animals have been published. In rabbits, approximately an amount of 1000 mg of diiodoxyquinoline per kg is lethal, and death occurred between 15 hrs. and 5 days after the administration (*Palm*).

David et al. (1933) observed that a single dose of 250 mg of vioform per kg caused deaths in rabbits. Seven out of 10 guinea pigs died when given single doses of 200 mg of vioform per kg (*David et al.* 1944). LD50 was determined at 175 mg per kg in guinea pigs and 400 mg per kg in kittens. No LD50 of diiodoxyquinoline could be established, because the mortality rate was not dose-related. Sporadic deaths occurred in the dose range of 50—2000 mg per kg.

Christensen & Dam (1961) observed kidney lesions in hamsters which had been given food to which 5,7-di-chloro-2-methyl-8-hydroxyquinoline (5,7-di-chloro-8-hydroxychinaldine, Sterosan) had been added. Lesions in the kidneys of rats given oxyquinoline (5,7-di-bromo-8-hydroxyquinoline and 5,7-di-chloro-8-hydroxychinaldine) were reported (*Meier-Ruge* 1963, 1964).

Vioform fed to white mice as an admixture of between 0.6 and 1 % caused convulsions and other nervous symptoms in some of the animals (*Püschner & Fankhauser* 1969). Degeneration and necrosis were observed in Ammon's horn.

Only few reports on the absorption and toxicity of oxyqui-

nolines in dogs have been published. *Tenney* (1936) mentions that a dose of 4—6 g of diiodoquin daily for 6 days did not cause symptoms of toxicity in dogs. No information is given on the breed or body size of his dogs.

Nervous symptoms in dogs and cats similar to those described by *Schantz & Wikström* (1965) and *Hangartner* (1965), apparently caused by therapeutic administration of hydroxyquinoline preparations, were reported by *Müller* (1967) and *Püschner & Fankhauser*. Acute poisoning attended with epileptic convulsions and chronic poisoning causing subacute myelo-optic neuropathy (S. M. O. N.) were produced experimentally in dogs, 1 cat, and 1 monkey given 60—144 mg of clioquinol per kg daily (*Tateishi et al.* 1971). Attempts to replicate these results in the laboratories of Ciba-Geigy were unsuccessful (*Cohn & Harun* 1972). Sandoz AG in Switzerland kindly provided results (unpublished) of toxicity studies on Intestopan in dogs (*Griffith* 1969). Dose levels corresponding to 100, 200, and 400 mg of broxyquinoline for 26 weeks 6 days a week were used. The SGPT levels were elevated, and hepatic lesions were observed at all dose levels. Sedation, ataxia, and paresis appeared in the 400-mg group.

Skin lesions such as furunculosis, erythema, and exudative dermatitis, have occurred after oral oxyquinoline treatment in man (*Silverman & Leslie* 1945, *Domar & Juhlin* 1967).

Since 1966, cases of optical-nerve atrophy and other neurotoxic effects, such as amnesia, after oxyquinoline therapy have been reported (*Berggren & Hansson* 1966, *Etheridge & Stewart* 1966, *Berggren et al.* 1968, *Strandvik & Zetterström* 1968, *Kaeser & Wüthrich* 1970, *Kaeser & Scollo-Lavizzari* 1970, *Kjaersgaard* 1971, *Bengtsson & Vikrot* 1972).

MATERIAL

Data concerning breed, age, sex, body weight, duration of intestinal symptoms before oxyquinoline treatment, oxyquinoline preparation and dose, and onset of symptoms are listed in Table 1. Most of the data are extracted from the history told by the owner of the dog. With the exception of a few cases, the case-histories were recorded by the present author, either at the admission of the dog, or later. It was completed at subsequent contacts. In many cases full information was not obtained at admission, because the owner was upset by the sudden disease of his dog.

RESULTS AND DISCUSSION

In Tables 2—5 the oxyquinoline group is shown together with 3 reference groups. Inpatients of the clinic during the period 1964—1969 (oxyquinoline cases excluded) cover the same period as the oxyquinoline group. Comparisons should be made mainly between these 2 groups.

At the analysis of the data (in 1970) it seemed important to obtain information on the distribution of licensed dogs in Stockholm, i.e. the great population to which most of the oxyquinoline cases belong. Unfortunately, such information was available only for the last year of the interesting sequence, namely 1969. In order to give a general idea of the correlation between this distribution and patients of the clinic, inpatients of 1969 are also shown.

Thirthy-two b r e e d s are represented in the oxyquinoline material (Tables 1 and 2), as against 94 in the inpatient material of the medical clinic during the corresponding period of time and 111 in Stockholm dogs. Different varieties of a breed are shown in Table 1. In Table 2 they are collected under 1 heading, i.e. the general name of the breed. The reason was that the exact variety of a breed to which a dog belonged was not always recorded in the Stockholm licence register or in some of the clinic's records. Some breed names noted in the Stockholm register do not even seem to be generally recognized and were presumed to be due to misunderstanding on the part of the owner. There are listed under the heading mongrels.

The Stockholm group comprises dogs which were licensed in 1969. It will be seen from Table 1 that only 2 oxyquinoline poisoning cases were diagnosed in 1969. Comparisons of breed distributions between 2 samples not covering the same period of time may be hazardous. From studying the record of the Swedish Kennel Club for the whole country it appears, for example, that in 1963 pekineses held position 13 among the most common breeds, but that in 1969 they had declined to position 20. Breed distribution in a population may thus change significantly within a few years, mainly because of changes in the public taste.

The number of dogs of some less common breeds is low in the oxyquinoline group — if represented at all — and low also in the reference groups. Discussions with expert statisticians (*Hessle* 1971) led to the conclusion that chi-square analysis would not be correct. Criteria considered to be compulsory for

Table 1. Survey of cases suspected of oxyquinoline poisoning, arranged chronologically from 1964 to 1969 (3 cases were actually admitted to the clinic in 1963). Names of breeds are identical with those in the breed register of the Swedish Kennel Club.

Case no.	Clinic no.	Breed	Age years	Sex	Body weight kg	Intestinal symptoms days*	Preparation used	Mg of oq. /kg body weight/day	Preparation given for number of days	First symptoms of intox.** hrs.	Recovered (R) Euthanized (E) Dead (D) days
1	109/63	Longhaired Dachshound	5	F	6.0	2	Enterovioform	83.3	2	unknown	R
2	467/63	Chow-Chow	1½	M	31.0	several	Entrokinol	32.3	unknown	<12	R
3	674/63	Miniature Poodle	10	M	14.5	1	Enterovioform	34.5	2	12	E (5)
4	27/64	Scottish Terrier	4	M	9.0	5	„	55.6	2	24	R
5	50/64	Airedale Terrier	5½	M	26.0	2—3	„	38.5	unknown	12—24	R
6	132/64	Wirehaired Dachshound	9	M	10.6	2	„	47.2	2	<24	R
7	193/64	Miniature Schnauzer	10	M	9.0	2	„	83.3	1	12	E (4)
8	207/64	Wirehaired Fox Terrier	6	M	8.0	2	„	62.5	2	<12	R
9	263/64	Wirehaired Dachshound	3	M	8.0	2½	„	125.0	1	6	R
10	268/64	Toy Poodle	2½	M	5.2	3	„	96.0	1	6	R
11	286/64	Smooth-haired Dachshound	13	F	8.0	1	Entrokinol	62.5	1	6—12	D (3)
12	302/64	Miniature Poodle	3	M	8.8	3	Enterovioform	85.2	1	6	R
13	310/64	Miniature Poodle	5½	M	12.4	3	„	40.3	1	6	R
14	367/64	Miniature Poodle	12	F	12.0	2—3	„	104.0	1	24	R
15	395/64	Scottish Terrier	9	M	13.7	2—3 hrs.	Intestopan	29.2	1	10	R
16	403/64	Smooth-haired Dachshound	7	M	9.5	1	Cholepur	157.9	1	24	R
17	405/64	Cocker Spaniel	12	M	16.5	21	Enterovioform	45.5	1	20	R
18	415/64	Smooth-haired Dachshound	11	M	9.6	7	„	26.0	1	2—3	R
19	437/64	Finnish Spitz	9	M	7.7	several	„	32.5	1	12	D (1)
20	686/64	Smooth-haired Dachshound	6	M	9.2	2	„	27.2	2	2	D (3)
21	705/64	Miniature Poodle	7	M	10.2	7	„	49.0	1	12	R
22	837/64	Alsatian	10	F	35.0	2	„	43.0	1	24	D (4)
23	934/64	Miniature Poodle	6	M	10.5	2—3	Intestopan	36.1	3	<24	E (1)
24	951/64	Papillon	5	M	2.0	1	Enterovioform	250.0	1	48	D (1)
25	953/64	Cocker Spaniel	8	M	18.8	6	„	26.6	1	2	R

* before administration of oxyquinoline (oq.).

** after the last dose where two or more doses were given.

Table 1. Continued.

Case no.	Clinic no.	Breed	Age years	Sex	Body weight kg	Intestinal symptoms days*	Preparation used	Mg of oq. /kg body weight/day	Preparation given for number of days	First symptoms of intox.** hrs.	Recovered (R) Euthanized (E) Dead (D) days
26	982/64	Welsh Terrier	5	F	10.6	1½	Enterovioform	23.6	1	⅓	R
27	28/65	Lakeland Terrier	3	F	8.0	2—3 hrs.	„	60.0	1	18	R
28	35/65	Wirehaired Fox Terrier	8	M	7.8	2—3 „	„	64.1	1	24	R
29	64/65	German Shorthaired Pointer	10	F	25.8	1	„	19.4	1	48	R
30	119/65	Wirehaired Fox Terrier	5	M	8.8	2—3 hrs.	„	28.4	3	unknown	R
31	148/65	Wirehaired Fox Terrier	12	M	7.3	2	„	68.5	1	12	D (11)
32	151/65	Elkhound	8	M	15.0	2	„	45.0	2	24	R
33	185/65	Toy Poodle	8	M	4.4	6	Sterosan	22.7	1	2—3	R
34	188/65	Miniature Poodle	6	M	8.8	unknown	Enterovioform	28.4	2	<24	R
35	190/65	Wirehaired Dachshound	11	F	6.7	„	„	37.3	1	10	E (9)
36	205/65	Miniature Poodle	7	F	9.0	1	„	55.0	1	<12	R
37	213/65	Alsatian	12	F	31.8	2—3 hrs.	„	23.6	1	12	R
38	250/65	Miniature Poodle	5½	F	7.0	14	„	71.4	2	16	R
39	268/65	Miniature Poodle	7	M	9.4	2	„	53.2	2	<24	R
40	271/65	Smooth-haired Dachshound	3	F	7.2	1	„	173.6	1	12—24	R
41	274/65	Toy Poodle	4	F	5.4	½	„	162.0	1	12	R
42	299/65	Smooth-haired Dachshound	9	M	10.0	2½	„	50.0	1	12	R
43	351/65	Cocker Spaniel	13	M	13.2	2—3 hrs.	„	37.9	1	12	R
44	357/65	Miniature Poodle	6	F	6.0	3	„	125.0	1	2—3	R
45	458/65	Saluki	3	M	26.0	4	„	28.8	1	12	R
46	502/65	Giant Schnauzer	⅔	M	28.5	7	„	35.1	2	<24	R
47	505/65	Toy Poodle	12½	F	5.8	2	„	86.2	1	4—6	D (6)
48	509/65	Toy Poodle	9	M	4.0	unknown	„	63.0	1	12	R
49	510/65	Toy Poodle	5	F	3.5	unknown	„	71.0	1	10	R
50	565/65	Miniature Poodle	10½	F	9.0	½	„	55.6	1	12—24	D (4)
51	575/65	Cocker Spaniel	9	M	17.4	½	„	28.7	1	6	E (3)
52	578/65	Boston Terrier	6	F	9.0	unknown	„	55.6	2	36	R

* before administration of oxyquinoline (oq.).

** after the last dose where two or more doses were given.

Table 1. Continued.

Case no.	Clinic no.	Breed	Age years	Sex	Body weight kg	Intestinal symptoms days*	Preparation used	Mg of oq. /kg body weight/day	Preparation given for number of days	First symptoms of intox.** hrs.	Recovered (R) Euthanized (E) Dead (D) days
53	589/65	Toy Poodle	6	M	8.4	2—3 hrs.	Enterovioform	59.5	1	48	R
54	796/65	Cocker Spaniel	2½	F	13.5	7	„	37.6	1	18	D (1)
55	842/65	Toy Poodle	1	M	4.0	7	„	125.0	2	2—3	R
56	968/65	Shetland Sheepdog	9	F	11.8	2	„	84.7	1	36	R
57	970/65	Giant Schnauzer	⅔	M	28.8	2	Sterosan	6.9	3	2	R
58	978/65	Toy Poodle	2	M	7.7	>3	Enterovioform	32.5	2	<12	R
59	1002/65	Cocker Spaniel	10	M	15.7	2	„	159.2	1	12	D (2)
60	/65	Whippet	10	F	10.0	3	„	25.0	1	5—6	D (<1)
61	/65	Golden Retriever	1½	M	23.2	7	„	10.8	1	11	D (<1 [2 hrs.])
62	/65	Mongrel	1	F	11.6	2	„	20—30 (taken as 25.0)	1	24	E (<1)
63	/65	Mongrel	9	M	30.0	—	„	100.0	1	16	D (1)
64	1/66	Smooth-haired Dachshound	1½	F	4.1	7	„	10.2	1	20	R
65	131/66	Mongrel	4	F	23.0	6	„	32.6	1	24	R
66	213/66	Smooth-haired Dachshound	10	F	9.1	1	„	109.9	2	24	R
67	222/66	Boston Terrier	6	F	9.0	2—3 hrs.	Mexaform	44.4	1	15	D (2)
68	322/66	Scottish Terrier	4	M	11.3	1	Fenilor	66.3	1	2½	R
69	349/66	Irish Setter	11	F	25.4	2—3	Enterovioform	29.5	1	2—3	D (3)
70	354/66	Pekinese	4½	M	4.3	2	„	29.1	1	2—3	R
71	373/66	Mongrel	2	F	11.2	2	„	44.6	2	2—3	R
72	493/66	Welsh Terrier	12½	F	10.2	3	„	16.3	3	24—36, —24***	R
73	944/66	Papillon	8	M	2.1	1	„	178.6	2	2—3	E (7)
74	1005/66	Scottish Terrier	2	M	11.6	1	„	43.1	1	20	R
75	1017/66	Golden Retriever	1½	F	23.4	6	Colepur	16.0	4	<48	R

* before administration of oxyquinoline (oq.).

** after the last dose where two or more doses were given.

*** refers to number of hours between onset of symptoms and administration of oq. (= last treatment). This dog also received oq. after the first symptoms had appeared.

Table 1. Continued.

Case no.	Clinic no.	Breed	Age years	Sex	Body weight kg	Intestinal symptoms days*	Preparation used	Mg of oq. /kg body weight/day	Preparation given for number of days	First symptoms of intox.** hrs.	Recovered (R) Euthanized (E) Dead (D) days
76	1063/66	Boxer	6	M	27.4	3½	Fenilor	30.4	3	12	E (3)
77	251/66o	Mongrel	10	M	30.0	2—3	Enterovioform	58.3	1	12	E (8 hrs.)
78	1324/66o	Alsatian	2	M	35.0	2—3	„	14.3	3	24	R
79	4409/66o	English Springer Spaniel	1½	M	20.0	2	„	12.5	2	24	R
80	233/67	Smooth-haired Dachshound	11	F	9.6	½	„	26.0	1	7	D (3)
81	364/67	Pekinese	7	F	5.0	7	„	200.0	1	8	R
82	446/67	Pekinese	8	F	6.2	14	„	80.6	1	5	R
83	482/67	Pomeranian	1	F	11.7	unknown	„	64.1	1	unknown	R
84	544/67	Elkhound	1½	M	20.0	—	Intestopan	40.0	1	„	R
85	549/67	Golden Retriever	2	M	27.5	2—3 hrs.	Entrokinol	18.1	1	2—3	R
86	558/67	Norwegian Buhund	5	F	16.0	2	Enterovioform	31.3	1	12	R
87	628/67	Smooth-haired Dachshound	4	F	9.5	7	„	39.5	2	10	R
88	719/67	Miniature Poodle	11	M	9.8	7	„	102.0	2	12	R
89	177/67o	King Charles Spaniel	1½	M	6.0	7	„	83.3	1	12	R
90	2047/67o	Labrador Retriever	7	F	30.0	14	„	27.8	3	12	D (1½)
91	122/68	Golden Retriever	6	M	45.6	5	„	49.3	2	2	R
92	218/68	Wirehaired Dachshound	3	M	9.0	2—3	„	83.0	1	12—24	R
93	228/68	Miniature Poodle	10	F	16.0	14	„	15.6	2	12	D (<24 hrs.)
94	413/68	Schnauzer	2	M	20.2	2	„	50.0	1	12	R
95	586/68	Longhaired Dachshound	1	F	5.5	½	Intestopan	27.3	1	6	R
96	670/68	French Bulldog	5	F	6.2	½	Mexaform	32.3	1	15	R
97	678/68	Cocker Spaniel	7	F	16.5	½	Enterovioform	15.2	1	2—3	D (24 hrs.)
98	711/68	Cocker Spaniel	12	M	18.4	3	„	40.8	2	<24, -8***	E (1)
99	778/69	Miniature Poodle	10	M	10.2	4	„	196.1	2	8	R
100	3617/69o	Smooth-haired Dachshound	15	F	9.1	2—3	„	27.5	1	8	E (10 hrs.)

* before administration of oxyquinoline (oq.).

** after the last dose where two or more doses were given.

*** refers to number of hours between onset of symptoms and administration of oq. (= last treatment). This dog also received oq. after the first symptoms had appeared.

Table 2. Breed distribution (% n) of dogs suspected of oxyquinoline poisoning as compared with all inpatients of the clinic in 1964—1969, and 1969, respectively, and with dogs licensed in Stockholm in 1969. Related breed varieties are collected under one heading, e.g. longhaired, wirehaired, and smooth-haired dachshounds under dachshounds.

Breed	Clinic inpatients 1964—1969 n = 4226	Clinic inpatients 1969 n = 468	Licensed Stockholm dogs 1969 n = 25580	Oxyquinoline patients 1964—1969 n = 100
Airedale Terrier	2.72	1.28	1.46	1
Alsatian	14.08	15.38	8.60	3
Boston Terrier	1.09	0.63	1.27	2
Boxer	8.75	10.25	4.52	1
Chow-Chow	0.59	0.21	0.65	1
Cocker Spaniel	4.63	2.35	3.04	8
Dachshound	17.01	13.46	18.06	17
Elkhound	0.43	0	0.36	2
English Springer Spaniel	0.38	0.63	0.19	1
Finnish Spitz	0.09	0.21	0.27	1
Fox Terrier	1.23	0.85	0.99	4
French Bulldog	0.71	0.42	0.75	1
German Pointer	0.38	0.63	0.26	1
Giant Schnauzer	0.17	0.21	0.20	2
Golden Retriever	0.59	1.71	0.56	4
King Charles Spaniel	0.02	0	0.10	1
Labrador Retriever	0.66	1.92	0.72	1
Lakeland Terrier	0.24	0.21	0.32	1
Miniature Schnauzer	0.28	0.42	0.55	1
Mongrel	6.93	4.91	8.89	5
Norwegian Buhund	0.02	0	0.11	1
Papillon	0.35	0.42	1.17	2
Pekinese	1.56	0.84	1.55	3
Pomeranian	0.33	0.21	0.59	1
Poodle	11.90	13.03	22.05	24
Saluki	0.19	0.42	0.17	1
Schnauzer	0.59	0.21	0.30	1
Scottish Terrier	1.37	1.70	1.00	4
Setter	0.71	1.07	0.46	1
Shetland Sheepdog	1.09	2.14	1.83	1
Welsh Terrier	0.17	0	0.52	2
Whippet	0.24	0.42	0.45	1

its use, e.g. absence of expected frequencies less than 1 (*Remington & Schork* 1970), are not fulfilled. Some suggestions may, nonetheless, emerge from non-computative comparisons of the columns.

The following breeds may be over-represented in the oxyquinoline material (see Table 2): foxterrier, Scottish terrier, Welsh terrier, papillon, pekinese, elkhound, cocker spaniel, golden retriever, giant schnauzer, and poodle. The poodles (toy and miniature) were small (cf. section on body weight). The three terrier breeds, papillons, and pekineses are small-size breeds. Cocker spaniel and elkhound are medium-size, whereas golden retriever and giant schnauzer are large-size breeds (see further below). There may thus be an excess of small-size breeds in the oxyquinoline material, which indicates that over-dosage of drugs might have been a factor concerned in causing disease. This assumption is in a way supported by Fig. 1, which shows a marked tendency of the dose, as mg per kg body weight, to rise as the dogs become smaller.

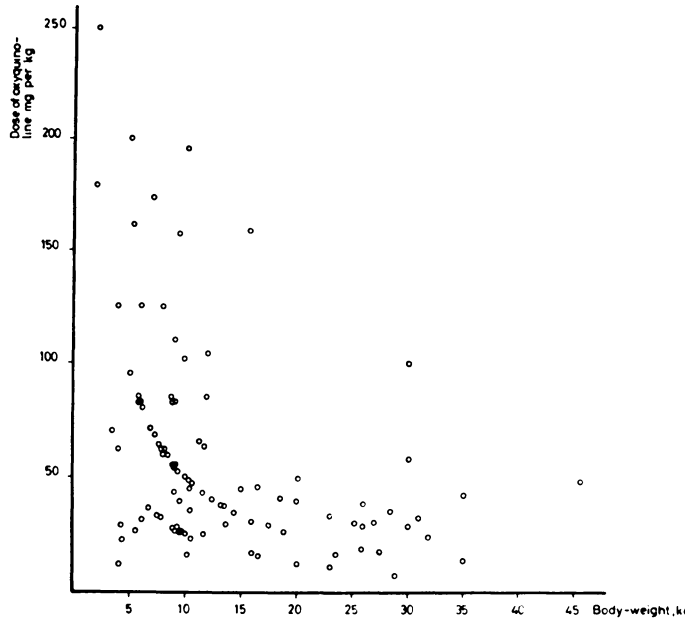


Figure 1. Relative doses of oxyquinoline, irrespective of preparation used, versus body weight. It appears that small dogs obtain higher doses than do large dogs.

The boxer and the Alsatian seem to be under-represented in the oxyquinoline material, when compared with the clinic material. However, a true interpretation is probably that these breeds are over-represented in the clinic groups. Boxers are known to have a high frequency of diseases, such as tumours, furunculosis, and CNS disturbances, and Alsatians are more than other breeds affected with gastrointestinal and skin diseases. The impression that the number of small-size breeds represented in the oxyquinoline group is higher than expected may therefore be false. It seems to be the effect of the frequent occurrence of large-size breeds in the clinic material (see further the section on body weight).

Table 3 shows the distribution by a g e in the 4 materials. It appears that the relative frequencies of the age-classes 2—7 years in the clinic materials are low in comparison with the

Table 3. Age distribution (% n). The mean age of the oxyquinoline group is higher than that of clinic inpatients in 1964—1969 ($P < 0.001$) and 1969 ($P < 0.01$) and licensed Stockholm dogs ($P < 0.005$). n = number of dogs whose ages were known.

Age years	Clinic inpatients 1964—1969 n = 4206	Clinic inpatients 1969 n = 465	Licensed Stockholm dogs 1969 n = 25405	Oxyquinoline patients 1964—1969 n = 100
< 1	14.38	14.62	3.17	2
1	12.70	12.26	11.34	11
2	9.06	8.82	11.10	8
3	7.04	6.45	12.18	6
4	5.99	4.30	10.56	6
5	6.75	6.67	9.81	10
6	7.35	6.45	8.75	10
7	6.80	7.10	8.31	7
8	8.23	8.17	6.93	6
9	5.85	7.10	5.31	8
10	6.73	7.31	4.19	12
11	4.02	3.66	3.16	4
12	2.95	3.66	2.24	7
13	1.33	2.58	1.39	2
14	0.55	0.22	0.82	0
15	0.19	0.22	0.42	1
16	0.07	0.44	0.20	0
>16	0.02	0	0.11	0
m. ± 1 s	5.457 ± 3.876	5.717 ± 4.049	5.697 ± 3.319	6.870 ± 3.709

Stockholm material, whereas there is some tendency towards the opposite at higher ages. This probably indicates that adult young dogs are healthier than older dogs. The low frequency of dogs younger than 1 year in the Stockholm material is probably an under-estimation due to the rule that only the birth year and not the exact age, e.g. 3 months, is recorded. The date of registration is February 1.

A comparison between the oxyquinoline and the control materials reveals some predonderance of higher age classes in the former. The age classes from < 1 year up to and including 4—5 years comprise approx. 50 % of the number of the dogs in the reference groups (Table 3), namely 49.2 % in inpatients over the period 1964—1969, 46.5 % in inpatients in 1969, and 48.4 % in the Stockholm dogs. Two large age classes were constructed, namely below and including 4—5 years and above and including 5—6 years. Chi-square analysis was applied to compare the oxyquinoline groups with inpatients in 1964—1969, using these 2 age classes. The difference is significant ($P < 0.005$).

The mean age of the oxyquinoline group is significantly higher than the mean values of the control group. This can be explained in 2 ways. Old dogs are more sensitive to oxyquinolines, or they are treated with such drugs more often than are young dogs. Both factors can of course cooperate. It is not the author's experience that older dogs develop incidental diarrhoea more frequently than do younger dogs. A more satisfactory hypothesis is that subclinical diseases, which interfere with the detoxification of oxyquinolines, are more frequent in the higher ages. Liver diseases of obscure aetiology are thus often observed.

Table 4. Sex distribution (% n). Analysis of frequencies (absolute numbers) in columns 2 and 3 (comparable years) shows $\chi^2 = 4.394$ ($P < 0.05$). This supports the assumption that males are over-represented in clinic inpatients, including oxyquinoline-poisoned dogs. n = number of dogs whose sex was known.

	Clinic inpatients 1964—1969 n = 4223	Clinic inpatients 1969 n = 467	Licensed Stockholm dogs 1969 n = 25541	Oxyquinoline patients 1964—1969 n = 100
Male	54.91	55.03	50.82	58
Female	45.09	44.96	49.18	42
Sex ratio	1.22	1.22	1.03	1.38

In the main, the liver seems to be the seat of the detoxicating processes.

The distribution by s e x is shown in Table 4. The over-representation of male dogs in the clinic material and in the oxyquinoline material in comparison with the Stockholm material seems to be undisputable. If true, the figures would show that male dogs are more often than female dogs affected with diseases that require consultation with the veterinarian. They would also indicate that male dogs may be more sensitive to oxyquinoline drugs.

The b o d y w e i g h t s of the dogs shown in Table 1 vary between 2 kg and 45.6 kg. The weight figures were divided into 4 classes: less than 9.0 kg, 9.0—17.9 kg, 18.0—26.9 kg, and more than 26.9 kg. The breed standard mean weights (Swedish Kennel Club) were used to construct the weights of the dogs in the control groups. Where such a standard weight was not available, or where the weight difference between the sexes of a breed is large, the mean body weight of dogs of the corresponding breed in the oxyquinoline material was used to determine the proper weight class of a breed.

Out of 24 poodles in the oxyquinoline material there are 9 toy poodles (mean body weight 5.38 kg) and 15 miniature poodles (mean body weight 10.24 kg). As the distinction between these varieties depends primarily on the height of the withers, a toy poodle may weigh more than a miniature poodle. For this reason, the mean weight for both varieties in common (8.42 kg) was used. All poodles of the oxyquinoline group were therefore included in the weight class less than 9.0 kg.

Information on the body weight of mongrels was only available for those in the oxyquinoline group (5 dogs, mean body weight 21.16 kg). The weights of mongrel dogs in the control groups could not be constructed, and they were therefore excluded.

The figures in Table 5 show that large dogs are over-represented in the clinic inpatients. There is no ground for the belief that oxyquinoline dogs deviate from the Stockholm dogs.

The time from the onset of intestinal s y m p t o m s (i.e. diarrhoea) to the start of oxyquinoline treatment varied between 2 hrs. and 21 days (Table 1). In 6 cases no information on the length of this time was available, and in 2 cases no intestinal symptoms had been observed. In 2 cases the owners did not re-

Table 5. Distribution of body weights (% n) of breeds represented in the oxyquinoline group, excluding mongrels. Analysis of frequencies (absolute numbers) in columns 1, 3, and 4 shows $\chi^2 = 100.041$ ($P < 0.001$), of frequencies in columns 1 and 4 $\chi^2 = 23.487$ ($P < 0.001$), and of frequencies in columns 1 (within brackets) and 4 $\chi^2 = 25.218$ ($P < 0.001$). The data support the assumption that large dogs are over-represented in clinic inpatients, as compared with the licensed Stockholm dogs and with oxyquinoline patients.

Body weight kg	1 Clinic inpatients 1964—1969 n = 3067 (3933)*	2 Clinic inpatients 1969 n = 334	3 Licensed Stockholm dogs 1969 n = 18691 (23305)*	4 Oxyquinoline patients 1964—1969 n = 95
< 9.0	46.60 (39.03)	41.83	63.48 (58.62)	58.95
9.0—17.9	13.13 (17.59)	10.73	12.20 (14.80)	23.16
18.0—26.9	6.04 (11.72)	5.65	3.48 (7.32)	5.26
> 26.9	34.23 (31.66)	41.58	20.88 (19.25)	12.63

* within brackets: all breeds (excluding mongrels).

member for how long symptoms had been seen before treatment was started, but "several" probably means more than 2 days. The time interval in the remaining 90 cases was less than 1 day in 16, between 1 and 3 days in 48 and more than 3 days in 26 cases. Thus, the disease preceding the oxyquinoline was generally of short duration.

During the period when the cases listed in Table 1 were observed, 11 oxyquinoline drugs were registered in Sweden as "proprietary preparations". Seven of them appear in the table. Enterovioform (clioquinol, 5-chloro-7-iodo-8-hydroxyquinoline) had been used in 85 cases, Intestopan (broxyquinoline, 5,7-di-bromo-8-hydroxyquinoline) in 4, Entrokinol (clioquinol) in 3, and each of Mexaform (clioquinol with bismuth), Sterosan (chlorquinaldol, 5,7-di-chloro-2-methyl-8-hydroxyquinoline), Colepur, and Fenilor (broxyquinoline) in 2 cases. Colepur, Fenilor and Intestopan, representing 8 % of the cases, contain only bromine of the halogens, and Sterosan (2 %) contains only chlorine. In Enterovioform, Entrokinol, and Mexaform, which were used in 90 %, there are chlorine and iodine in the molecule. All halogens are thus represented. As mentioned above, Enterovioform was predominant among the oxyquinolines used. It has not been possible to obtain detailed information regarding the relative parts of the market covered by the various preparations. Ac-

cording to estimations by representatives of some of the largest pharmacies in Stockholm, Enterovioform was used much more than any other oxyquinoline. Obviously, the present data do not support the assumption that Enterovioform would be more toxic to dogs than other oxyquinoline drugs.

The daily dose of oxyquinoline (Table 1), irrespective of preparation used, could be more or less exactly confirmed from the history. The dose varied between 6.9 and 250 mg per kg body weight. Mean value ± 1 s is 58.98 ± 46.60 mg. There is a significant skewness in the dose sample, 65 doses being less than the mean value. The skewness is due to the fact that very large doses were given in a small number of cases. Thus 14 dogs received more than 100 mg and 8 dogs more than 150 mg per kg.

Recommended daily doses to man of the oxyquinoline drugs listed in Table 1 range from 600 to 2400 mg. This corresponds to 8.5—34 mg/kg and 10.9—43.6 mg/kg, respectively, at an assumed body weight of 70 kg and 55 kg. The median dose in the oxyquinoline group is 43.75 mg per kg. Though there were no doses recommended for dogs, this supports the belief that oxyquinoline intoxication is not simply a matter of over-dosage.

The duration of oxyquinoline therapy was 4 days in 1 case but no more than 3 days in the others. In 66 dogs, the drug was given for only 1 day. (Information was lacking in 2 cases.) Oxyquinoline administration resulting in intoxication was thus of short duration. It should be mentioned here that, according to the case histories, several dogs had been treated with an oxyquinoline drug earlier without developing any symptoms of intoxication.

The time interval from the last oxyquinoline administration to onset of toxicity symptoms varied from 20 min. to 48 hrs. In 4 cases the length of this interval could not be calculated, because of incomplete information. Although the total dose given in 1 day could usually be well confirmed from the owner's information, it often proved difficult to find out, whether this dose had been given on 1 occasion or as fractions of the dose 2 or more times. Therefore, in a single case, in which treatment had been performed just for 1 day, it cannot be concluded that the time interval in the last but one column of Table 1 really represents the interval from "responsible" dose to onset of symptoms. By chance, in the case where the interval was as short as 20 min. it could be convincingly established that the

drug had been administered only once. In nearly two-thirds of the cases the time interval was 12 hrs. or less and in approx. four-fifths less than 24 hrs. The median is 12 hrs. This again supports the hypothesis that in dogs oxyquinoline poisoning is a very acute event, provided that the metabolic conditions are favourable.

The eventual outcome was recovery in 70, death in 19, and euthanasia in 11 cases. Death occurred after an interval varying from 2 hrs. to 11 days after the last administration of oxyquinoline. The corresponding interval for euthanasia was 8 hrs. to 9 days. Euthanasia was performed where death was estimated as highly probable. The therapeutic measures undertaken will be described (*Lannek*, to be published).

Breeds contributing with more than 1 dead dog were dachshound (5/17), poodle (5/24), cocker spaniel (5/8), and papillons (2/2) (ratio dead/total within brackets). The 2 papillons, which were the smallest dogs of the group, had been given very high relative doses of oxyquinoline, 250 and 178.6 mg per kg.

The mean age of 30 dead dogs was 8.70 ± 3.34 (m. ± 1 s) years as against 5.52 ± 3.39 years in recovered dogs. The difference is significant ($P < 0.001$). This again supports the assumption that old dogs would be more vulnerable to oxyquinolines than young dogs. The decision to perform euthanasia was not influenced by the age of the dog. The mean age of dogs which died spontaneously was 8.58 years.

The sex ratio in dead dogs was 1:1, as against 1.38 (most males) in the whole group. The age of 10 of the dead bitches exceeded the mean age (8.7 years) of dead dogs.

The body weight of dead dogs varied from 2 to 35 kg. The distribution within weight classes (cf. Table 5) is 50.0, 23.3, 13.3, and 13.3 % which compares fairly well with the distribution within the whole group, namely 58.95, 23.16, 5.26, and 12.63 %. Any higher sensitivity in small-size dogs (cf. above) is thus not reflected by a higher mortality rate.

The duration of intestinal symptoms was roughly the same in dead dogs and in recovered dogs. Thus, in each of the groups the duration was 1 to 3 days in about 50 %.

Five oxyquinoline drugs out of a total of 7 were given to dogs which subsequently died, namely Enterovioform (26), Entrokinol, Fenilor, Intestopan, and Mexaform (1 of each). This distribution is closely similar to that for recovered dogs. Dead

dogs had not been given larger doses of oxyquinolines (mean value 56.57 mg per kg) than had recovered dogs (60.02 mg per kg). This supports the conception that the toxicity of oxyquinolines in dogs is not dose-related under the conditions studied.

Nor is there any observable difference in the number of days for which oxyquinoline drugs had been given or in the interval between the last administration and onset of symptoms.

CONCLUSIONS

Recent investigations confirm the opinion that halogenated oxyquinolines are absorbed from the intestine in significant amounts. Toxic symptoms have been observed in man, dogs, cats, and in a number of laboratory animal species.

The present survey of intoxications in dogs due to deliberate administration of oxyquinolines does not reveal any breed predisposition. The frequent occurrence of some breeds, e.g. dachshound and toy and miniature poodle (41 out of a total of 100) corresponds to the distribution of dogs in Stockholm and of inpatients at the clinic. On the other hand, the rare occurrence of Alsatians and boxers in comparison with the total material of inpatients is explained by their over-representation in the latter material. Some rather common breeds, e.g. collie and drever, are not represented at all in the oxyquinoline group. One cannot expect, however, that a fairly small sample like the oxyquinoline group will represent the population closely.

The mean age in the oxyquinoline group was 6.87 years, as against 5.46—5.72 years in the reference groups. This indicates a greater tendency for older dogs to develop the disease. Correspondingly, the mean age of dead dogs was higher than that of recovered dogs. There is no indication that one of the sexes would be more frequently affected than the other one.

Fifty % of the dogs in the oxyquinoline group had been given daily doses not exceeding 43.75 mg per kg, mostly for one or a few days before the onset of disease. If this dosage is compared with that recommended for man and with the amounts usually tolerated by healthy experimental dogs, it is apparent that the acute disease is not caused simply by over-dosage.

Obviously, the most important factor that determines whether or not diseases will develop is not the magnitude of the dose. Healthy experimental dogs will normally tolerate single doses of 1000 mg per kg body weight without showing any symptoms of

disease (*Lannek & Lindberg*, to be published). On the other hand, a single dose of the order of 10 mg per kg may under some conditions cause a lethal disease. All dogs (excluding two) presented in this paper had mild diarrhoea at the time they were given an oxyquinoline drug. It is then tempting to assume that a diarrhoeal condition may increase the dog's sensitivity to oxyquinolines.

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SAMMANFATTNING

Toxiciteten av oxikinoliner hos hund. En klinisk studie. I. Kasuistik.

En översikt av 100 fall av oxikinolinförgiftning hos hund presenteras. Sjukdomen som har ett akut förlopp karakteriseras bl. a. av ökad retbarhet i CNS samt myokard- och leverskador. Mortaliteten (avlivade hundar inkluderade) var 30 %. Enligt anamnetiska uppgifter hade oxikinolinbehandlingen, som föregick sjukdomen, utförts p. g.a. att hunden hade tillfällig diarré. I flertalet fall hade preparatet givits endast 1 dag innan hunden insjuknade. Medianen (avseende tiden från sista dosen till symtomens uppträdande) var 12 timmar. Gamla hundar insjuknade oftare och visade högre mortalitet än de yngre hundarna.

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