Dieldrin poisoning in dogs: relation to obesity and treatment

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Keane, William T., Zavon, Mitchell R., and Witherup, Samuel H. (1969). *Brit. J. industr. Med.*, 26, 338-341. **Dieldrin poisoning in dogs: relation to obesity and treatment.** The time interval required for poisoning to result in mammals from the prolonged absorption of a relatively constant amount of dieldrin, a chlorinated hydrocarbon insecticide, is directly related to obesity. This relationship should be applicable regardless of the route of absorption of dieldrin (ingestion, inhalation, or percutaneous). Forced feeding of a high calorific value food appears to have a place in the treatment of dieldrin poisoning and, by extension, in the treatment of poisoning from many other chlorinated hydrocarbon insecticides.

Very little research has been undertaken with toxic agents to examine the relationship of weight loss and/or obesity to poisoning. This lack is nowhere more obvious than with the chlorinated hydrocarbon insecticides, as these compounds are stored primarily in the adipose tissue of the mammal and it is reasonable to suppose that the dynamics of the fat depot may influence the rate of onset or the intensity of poisoning. This aspect has been rarely dealt with even for dieldrin, one of the most thoroughly investigated of the chlorinated hydrocarbon insecticides. Heath and Vandekar (1964) reported a marked increase in the excretion of ³⁶Cl-dieldrin in rats after short periods of starvation. They stated, 'The obvious inference is that the concentration of dieldrin in the blood stream is increased when the fat is mobilized from its depots'. Barnes and Heath (1964) studied the factors affecting the LD₅₀ of dieldrin in rats. They observed that rats surviving a toxic dose lost weight and were more susceptible to a second dose during this period.

The treatment of dieldrin poisoning has been largely symptomatic - lavage, sedation with barbiturates, and supportive therapy. As an incidental result of experiments in which dieldrin was ad-

ministered to dogs until they became poisoned, a new method of treatment has been discovered which may be applicable to humans.

Materials and methods

Eighteen mature dogs, 24 to 27 months of age, were divided by a standard random sampling technique into three groups of six dogs each (Table 1).

The active constituent of dieldrin, 1,2,3,4,10,10-hexachloro - exo - 6,7 - epoxy - 1,4,4a,5,6,7,8,8a-octahydro-1,4-endo,exo-5,8 dimethanonaphthalene, was recrystallized. Its m.p. and chromatography gave its purity as greater than 99%. It was dissolved in corn oil and enclosed in gelatin capsules (size 000). The most put into

TABLE 1
DOSE SCHEDULE

Group	No. of dogs/group	Sex	Dose of dieldrin (mg./kg./day)	Duration (days)
Control	6	5M, 1F	0	0
Acute	6	4M, 2F	2.0	0-intoxication
Subacute	6	4M, 2F	1.0	0-5
			0.2	6-62
			2.0	63-intoxication

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any capsule was 1.2 ml., and only one capsule was fed to each animal every day. The daily dose was adjusted to the body weight of the dog based on the previous week's weight. The dose was fed to each dog five days a week until signs of poisoning were observed. The dog food was analysed for dieldrin, but none was detected within the limits of sensitivity of the analytical method used (1 ng./g.).

The total body fat may differ significantly from animal to animal. To determine the lean body mass (LBM) and hence the fat content of the animals, the indirect quantitative method of Forbes (1962) was employed. Most of the potassium present in the mammalian body is stored intracellularly. Naturally occurring radioactive potassium (^{40}K) comprises 0.012% of the total body potassium. Measurement of the ^{40}K with a whole-body counter allows calculation of the total potassium and in turn calculation of the LBM which is related to the potassium present, assuming that the LBM has a constant potassium content and that neutral fat does not contain electrolytes. It also depends upon the use of a conversion factor, derived from a paper by Moore, Muldowney, Haxhe, Marczyńska, Ball, and Boyden (1962) on dogs, with the factor employed for calculating human lean body mass (68.1 mEq K/kg. LBM) by Forbes, Gallup, and Hursh (1961). To determine the LBM the dog was anaesthetized with Demerol (meperidine hydrochloride, 5 mg./kg. body weight), atropine (0.02 mg./kg. body weight), and Surital (sodium 5-alkyl-5(1-methylbutyl)-2-thiobarbiturate, 0.7 ml. of 2.5% aq. solution/kg. body weight). It was then placed in a large plastic bag loosely tied about the neck, and placed in a whole-body counter for a three-hour counting period. The counts were recorded via a sodium iodide crystal 8 in. (20 cm.) in diameter and 4 in. (10 cm.) thick, which was placed 40 cm. above the dog, by 200 channels of a 400-channel analyser, which were used to count all particles with energies in the range 1.30 to 1.54 MeV. The results were compared with standard dog phantoms counted for one hour. These phantoms were made of 2-lb. (0.9 kg.) boxes containing sugar and a known quantity of potassium chloride. A separate phantom was constructed to resemble each animal. The total body fat of each animal (Table 2) was determined by subtracting the LBM at the end of the experiment from the body weight recorded at the beginning of the experiment. This assumes a constant LBM, an assumption which may be invalid. However, as the animals had lost weight during the development of poisoning, reference to the body weight during or after the development of poisoning would have obscured the relationship being investigated, *i.e.*, that between obesity at the beginning of exposure and the length of time required for poisoning to develop.

The total body water space was determined by an isotope dilution technique (tritiated water) in order to rule out the presence of oedema which would have invalidated the previously stated assumptions. None of the animals was found to be oedematous.

The concentration of dieldrin in the blood of all animals was measured biweekly throughout the experiment using a gas-liquid chromatograph equipped with an electron-capture detector.

Dogs were only regarded as grossly poisoned when they

TABLE 2
NUMBER OF DAYS UNTIL OCCURRENCE OF FIRST MUSCULAR SPASM AND GROSS INTOXICATION, AND TOTAL KILOGRAMS ADIPOSE TISSUE IN EACH DOG AT BEGINNING OF EXPERIMENT

Dog	Dog body weight (kg.)	Total fat in body (kg.)	Days until intoxication ¹	Days until first muscular spasm
<i>Acute group</i>				
7	16.85	5.73	67	50
16	12.11	2.31	50	30
14	9.45	1.72	59	25
3	10.21	1.66	45	24
17	11.80	1.55	45	37
10	9.68	—	35	31
Means		2.59	50	33
<i>Subacute group</i>				
4	15.39	5.96	85 ²	74 ²
1	10.81	2.21	45	38
18	10.89	1.95	24	23
13	9.46	1.34	28	27
9	9.98	1.04	25	17
8	7.54	0.63	18	15
Means		2.19	38	32

¹Three animals failed to exhibit convulsions but were judged to be intoxicated.

²Counting of days began on day 63 when dose was increased to 2.0 mg./kg./day.

showed widely disseminated muscular spasms or convulsions. The first muscular spasm was, however, also recorded.

Results

Dieldrin intoxication and obesity

Gross poisoning was always preceded by a decrease in food consumption and body weight and by the first muscular spasm.

The number of days of dieldrin ingestion required to produce both gross poisoning, as defined above, and the first muscular spasm was directly related to the fat content of the animal at the beginning of the experiment (Table 2).

In each dog of the 'subacute' group the dieldrin concentration in the blood stayed fairly constant from day 7 to day 59 (the last day a blood sample was analysed before increasing the dose to 2.0 mg./kg./day), indicating equilibrium of dieldrin between fat and blood (Keane and Zavan, 1969a,b). During this period the concentrations in the blood were all in the range 7.2–19.2 $\mu\text{g.}$ dieldrin/100 mg. whole blood. The consistently low blood levels were observed in the obese animals and the high blood levels

were observed in the lean animals (on day 50 a correlation coefficient of -0.90 existed). Table 2 shows that in most instances pretreatment with 0.2 mg./kg./day (the 'subacute' group) reduced the time interval before the onset of poisoning, presumably because the dogs treated in this way became leaner.

Dieldrin poisoning and treatment

As stated previously, all animals ate less before showing clinical signs of poisoning. Marked anorexia was observed only in four of the most lean dogs. The first dog to become poisoned in this manner was dog no. 10. This animal was the first in the acute group to become grossly poisoned, which would suggest from the results in the previous section that it was the most lean in this group, and accorded with visual observations. This animal was treated in the conventional symptomatic manner with sodium barbiturate for five days, but death occurred in spite of treatment. Death prevented the estimation of total body fat in this animal but Tables 3 and 4 show that after the onset of gross poisoning the body weight progressively decreased and the concentration of

dieldrin in the blood progressively increased. The anorexia and associated fat mobilization appeared to interfere with the absorption of dieldrin from the blood into the fat, thus intensifying the poisoning. Since the fat so mobilized contained a high concentration of dieldrin, the poisoning which caused the anorexia then became self-perpetuating. It seemed possible that this process might be reversed by forcefully preventing the mobilization of the fat stores. To test this hypothesis the next three animals exhibiting marked anorexia were treated *only* by force feeding an amount of commercial canned dog food calculated to be in excess of the normal calorific requirement. This was accomplished by refrigerating the food, which could then be cut into semi-solid boluses. These were individually force fed, by hand, on numerous occasions each day. Tables 3 and 4 show that after the onset of gross poisoning the body weights of these animals progressively increased and the concentrations of dieldrin in the blood progressively decreased. All of these dogs recovered even though forced feeding was the *only* form of treatment administered.

TABLE 3
DOG BODY WEIGHTS (KG.) BOTH BEFORE AND AFTER THE ONSET OF GROSS POISONING

Dog		Before poisoning				After poisoning			
10	Days	24	17	10	3	4	11	14	
	Body weights ..	9.06	9.12	8.92	7.48	6.38	5.56	Dead	
9*	Days	27	20	13	6	1	8	15	22
	Body weights ..	9.51	9.08	9.51	8.79	7.88	8.62	9.82	10.32
8*	Days	27	20	13	6	1	8	15	22
	Body weights ..	7.40	7.24	7.30	7.32	6.23	6.10	7.42	7.84
17*	Days	27	20	13	6	1	8	15	22
	Body weights ..	11.32	10.98	10.56	9.92	10.06	10.53	10.63	10.74

* These dogs were forced-fed after onset of poisoning.

TABLE 4
CONCENTRATION OF DIELDRIN IN BLOOD BOTH BEFORE AND AFTER POISONING
($\mu\text{g.}/100$ g. WHOLE BLOOD)

Dog		Before poisoning				After poisoning			
10	Days	14	11	7	4	3	7	10	14
	Dieldrin in blood..	46	36	89	65	117	132	167	Dead
9	Days	13	9	6	2	1	5	8	12
	Dieldrin in blood..	31	54	52	48	93	123	117	76
8	Days	14	10	7	3	4	7	11	14
	Dieldrin in blood..	44	51	40	70	113	96	82	55
17	Days	14	10	7	3	4	7	11	14
	Dieldrin in blood..	47	57	69	79	79	71	62	56

Discussion

The experiment reported here supports the hypothesis that, for equal doses of a chlorinated hydrocarbon insecticide, the size of the fat depot in the exposed animal directly determines the duration of exposure required to produce overt poisoning (Table 2).

Forced feeding saved the lives of three dogs which were expected to die after the onset of poisoning from dieldrin. We believe that the mechanism underlying the success of the forced feeding therapy was that it increased body weight and decreased fat mobilization thereby simultaneously decreasing the concentration of dieldrin in the blood. This physiological approach to therapy combined with the conventional pharmacological method should be clinically evaluated.

Before overt intoxication the body weight decreases due to anorexia and this is accompanied by an associated increase in the concentration of dieldrin in the blood. Once the critical concentration of dieldrin in the blood is exceeded, poisoning develops. This supports the hypothesis which Heath and Vandekar (1964) previously presented to explain the increased rate of excretion of ^{36}Cl -dieldrin in rats following restricted dietary intake. These results may support the postulate of Heath and Vandekar (1964) that dieldrin released from fat mobilized during periods of weight loss was possibly responsible for the delayed poisonings reported by Hayes (1957, 1959), who examined men engaged in dieldrin spraying operations.

This phenomenon of delayed poisoning in humans could only occur if the concentration of dieldrin in their blood was very close to the critical concentration required for poisoning and if their adipose tissue possessed unusually high concentrations of dieldrin as a result of an occupational exposure in

which extremely inadequate industrial hygiene was the rule. With regard to the general population, research conducted by Hunter and Robinson (1968) indicated that individuals, non-occupationally exposed to dieldrin, would not become poisoned even during periods of extreme weight loss.

Though extreme caution must be exercised in extrapolating the results of this animal experimentation to man, we believe that there is sufficient information available, both theoretical and experimental, to justify a clinical trial of forced feeding in the event of a case of acute poisoning by a chlorinated hydrocarbon insecticide in man.

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