Drug Effects on Dieldrin Storage in Rat Tissue*

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The accumulation of certain insecticides or their metabolites in the animal body following the consumption of contaminated feed is one of the greatest detriments to the use of insecticides in the production of food or forage crops. Members of the chlorinated cyclodiene insecticides, e.g., dieldrin, aldrin, endrin, and heptachlor, represent the greatest potential problem because of their relatively great storage rates in animal tissues (1).

We recently obtained a marked reduction in dieldrin storage in rat tissue in our laboratory by administering DDT (2). This effect had apparent parallels in the well established affects of DDT and certain other compounds which stimulate the detoxification rates of a variety of drugs (3,4). These similarities led us to test selected drugs for their effectiveness in reducing dieldrin storage in rats.

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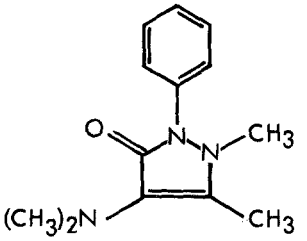
Experimental

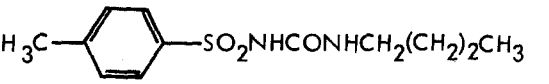
The selected drugs, which are neither chemically nor pharmacologically related, are shown in figure 1‡. Aminopyrine and phenylbutazone are antipyretic and analgesic agents, heptabarbital is a sedative and tolbutamide is an antidiabetic. Each, however, stimulates the metabolic detoxification rate of some other drug. For example, aminopyrine (5), phenylbutazone (5), and tolbutamide (4) stimulate hexobarbital detoxification, phenylbutazone and aminopyrine (5) stimulate zoxazolamine detoxification and heptabarbital stimulates the metabolism of certain coumarin anticoagulants (6).

Individual female rats were fed a basal diet containing 1 ppm dieldrin (in one trial the feed contained 10 ppm dieldrin). The drugs were administered as feed additives or by i.p. injections. A negative control, consisting of a group treated only with dieldrin, and a positive control group which was treated with dieldrin plus DDT, were included in each experiment. Five rats were in each treatment group. The rats were sacrificed

‡ The drugs used were generously supplied by the following companies: aminopyrine, Sterling-Winthrop Research Institute; heptabarbital and phenylbutazone, Geigy Research Laboratories; tolbutamide, The Upjohn Company.



Aminopyrine



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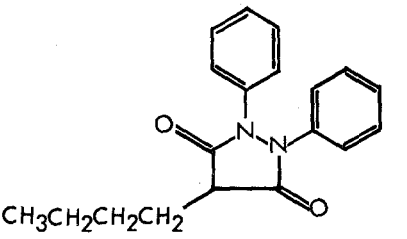
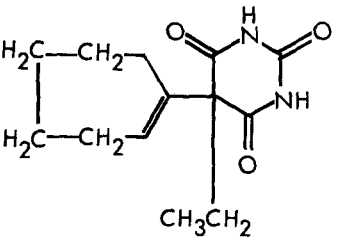


Phenylbutazone



Heptabarbital

Figure 1. Drugs tested for effectiveness in reducing dieldrin storage in rat tissue.

after 10 days of treatment. Abdominal adipose tissue was analyzed for lipid content by a dichromate oxidation procedure. Residual dieldrin was determined by electron capture gas chromatography. These methods have been described in an earlier paper (2). Analysis of variance techniques were used to aid in interpreting results.

Results and Discussion

Results of the drug tests are summarized in tables 1-3. The concentration of dieldrin found in adipose tissue, as ppm in tissue lipids, is listed and also the storage reduction relative to control rats that received only dieldrin. Each drug caused a significant reduction in dieldrin storage when administered in the diet (tables 1 and 2). The groups treated with low drug levels had

TABLE 1

Drug effects on dieldrin storage. All rats received 1 ppm dieldrin in the diet continuously for 10 days. Dosages are listed as daily intakes per kilogram of body weight

Treatment	Tissue dieldrin		Storage reduction
	µg/g lipid	±SE	%
Control	7.53	0.89	
DDT, 4 mg/kg	2.06	0.34	72
Tolbutamide, 60 mg/kg	6.54	0.47	13
Tolbutamide, 290 mg/kg	3.20	0.72	57
Aminopyrine, 75 mg/kg	2.76	0.39	63
Aminopyrine, 350 mg/kg	1.40	0.09	81
Heptabarbital, 40 mg/kg	4.01	0.67	47
Heptabarbital, 225 mg/kg	1.50	0.07	80

TABLE 2

Effects of phenylbutazone on dieldrin storage. Series A: All rats received 10 ppm dieldrin in the diet continuously for 10 days. Series B: All rats received 1 ppm dieldrin in the diet continuously for 10 days. Dosages are listed as daily intakes per kilogram of body weight

Treatment	Tissue dieldrin		Storage reduction
	µg/g lipid	±SE	%
A. Control	74.2	10.1	
Phenylbutazone, i.p. 50 mg/kg, 4 days	75.7	1.5	0
DDT, i.p. 20 mg/kg, 3 days	18.0	3.2	76
B. Control	9.38	0.67	
Phenylbutazone, fed 90 mg/kg, 10 days	5.68	0.95	39
DDT, fed 4 mg/kg, 10 days	1.97	0.33	79

dieldrin residues significantly lower than the control group. The dieldrin residues were significantly higher, however, than in the high drug dosage groups. This suggests that normal dose-response relationships occur with this phenomenon. Although the tests were not designed for an accurate comparison of potencies, the drugs appeared to rank in the following order: heptabarbital > aminopyrine ≫ tolbutamide. Phenylbutazone was tested in a different trial and showed a potency similar to tolbutamide. Heptabarbital, the most potent, caused an 80 per cent reduction in tissue dieldrin con-

centration when given at the level of 225 mg/kg body weight for 10 daily doses. DDT, about 50 times more effective than heptabarbital, was far more potent than any of the drugs.

Some data indicated that the drug effect is either slowly activated or is of transient duration. In our initial experiment, phenylbutazone given i.p. for 4 days was ineffective but later proved to be active when fed for ten days (table 2). Possibly the longer time period was necessary in order for the effect to become fully activated. However, DDT was very effective after only 3 days of i.p. administration which is another contrast between the activity of DDT and the drugs. Somewhat similar observations were made with aminopyrine (table 3). When administered i.p. for 5 days it was less effective than when lower dosages were given the entire 10 days. Significant reductions of dieldrin storage were obtained, however, with the 5-day treatment schedule for all but the lowest aminopyrine dose level. Either the effect had diminished after the fifth day, or the mechanism was not fully activated during the 5-day period. A study of the relative potencies of these drugs and DDT and the duration of their effects is continuing in our laboratory.

TABLE 3

Effect of Aminopyrine on dieldrin storage. All rats received 1 ppm dieldrin in the diet continuously for 10 days. Dosages are listed as daily intakes per kilogram of body weight

Treatment	Tissue dieldrin		Storage reduction
	µg/g lipid	±SE	%
Control	6.36	0.50	
Aminopyrine, 10 days, i.p.			
25 mg/kg	6.30	0.62	0
50 mg/kg	4.92	0.64	22
75 mg/kg	3.66	0.15	42
Control	7.61	0.63	
Aminopyrine, 5 days, i.p.			
50 mg/kg	7.97	0.27	0
100 mg/kg	5.71	0.64	25
150 mg/kg	6.51	0.24	15

Others have recently reported similar results from the use of phenobarbital. Cueto and Hayes found reduced amounts of dieldrin-derived material in the fat of rats under chronic phenobarbital-dieldrin treatment as compared to rats treated with dieldrin alone (7). Koransky et al. reported a marked acceleration in elimination of BHC metabolites when rats were pretreated with phenobarbital (8).

These various drugs, including phenobarbital and DDT, are thought to stimulate detoxification reactions by inducing synthesis of hepatic microsomal enzymes which participate in the metabolism of lipid-soluble

compounds (9). It is significant that dieldrin metabolism is affected by these non-specific agents and it is likely that the effects can be demonstrated with other members of the chlorinated cyclodiene insecticides and BHC, and in other animal species. These observations may lead to the development of agents which will safely reduce insecticide accumulation in the tissues of animals and man. Such agents might also be used for the treatment of individuals who may become over exposed to insecticides.

Summary

Selected drugs were tested for effectiveness in reducing dieldrin retention by rats. Female rats were fed diets treated to contain 1 ppm dieldrin. The drugs were administered as feed additives or by i.p. injections. The rats were sacrificed after 10 days of treatment and abdominal adipose tissue was analyzed for dieldrin using electron capture gas chromatography.

Heptabarbital (40 and 225 mg/kg rat/day), aminopyrine (75 and 350 mg/kg rat/day), tolbutamide (60 and 290 mg/kg rat/day), and phenylbutazone (90 mg/kg rat/day) were effective as feed additives in reducing tissue dieldrin. Heptabarbital was the most effective and reduced the concentration of tissue dieldrin by 80 per cent at the higher dose level. In comparison, DDT

(4 mg/kg rat/day) effected a 72 per cent reduction. A contrast with DDT was also observed in trials with i.p. administration of drugs and DDT. In those trials, the duration of the DDT action was apparently greater than that of the drugs.

We suggest that suitable drugs might be used to reduce insecticide accumulation in the tissues of animals and man, and for treatment of individuals after over exposure to insecticides.

Acknowledgements

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