Convulsive Action of Small Single Oral Doses of the Insecticide Lindane

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The effects of lethal or near-lethal doses of the insecticide lindane (γ-hexachlorocyclohexane) on the nervous system were recognized early (Dallemagne and Philippot, 1948). The primary symptoms in acute lindane poisoning include hyperexcitability, tremors and convulsions. Although seizures following accidental ingestion of very small amounts of lindane have been observed in man (Hayes, 1965), there is no experimental evidence for convulsive action of lindane in small doses.

In a pilot study with a quite different purpose, we have observed 1-3 minute long seizures in rabbits given small oral doses of lindane. The seizures were of the grand mal character, and occurred chiefly in connection with copulation. They could also easily be elicited by exposure to stroboscopic light.

In the experiments reported here, we have administered lindane orally in small doses to mice and then examined changes in seizure threshold by means of pentylenetetrazol, a drug used in determining convulsive properties of different pharmaca (Goodman and Gilman, 1970).

Material and methods

Lindane (1,2,3,4,5,6-γ-hexachlorocyclohexane, purum) was obtained from Schuchardt, München, Germany and pentylenetetrazol from Sigma Chemical Comp., St. Louis, U.S.A.

Adult female albino mice (NMRI strain from Anticimex, Solna,

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Sweden) weighing around 25 g were used as experimental animals. They were allowed free access to food (pellet 210 from Astra--Ewos, Södertälje, Sweden) and tap water during the experimental period.

Lindane was dissolved in peanut oil in concentrations from 2 to 0.25 mg/ml and was administered orally to the animals by means of a tube. Corresponding amounts of peanut oil were given to the control animals.

Pentylenetetrazol was dissolved in water at a concentration of 4 mg/ml. The sensitivity of the mice to the drug was determined by intravenous injections of pentylenetetrazol at a dose of 20 mg/kg body weight. This dose caused seizures in about 15 % of the control animals. The requisite amount of pentylenetetrazol was injected rapidly in a tail vein, the duration of injection not exceeding 3 seconds. Immediately following the injection the animals were quickly withdrawn from the injection box for observation. The occurrence of convulsions or singular twitchings were noted. Animals showing neither convulsions nor twitchings were classified as unaffected.

Two experiments were carried out, the first to examine the sensitivity to pentylenetetrazol at various times after the administration of lindane, and the second to establish the lowest dose of lindane affecting the sensitivity.

In the first experiment lindane was administered orally to 6 groups of mice at a concentration of 10 mg/kg body weight. 6 groups of control animals received the same amount of peanut oil. Pentylenetetrazol was injected 1, 2, 3, 6, 12 and 24 hours after the lindane administration.

In the second experiment, 6 groups of mice received different concentrations of lindane, 10, 7.5, 5, 2.5 and 1.2 mg/kg body weight. The sixth group received only peanut oil. Pentylenetetrazol was injected 3 hours later.

Results

Table 1 gives the results when the pentylentetrazol seizure threshold was tested at various times after administering a single dose of 10 mg lindane/kg body weight. The sensitivity to pentylenetetrazol increased rapidly to reach a peak after three hours, when 80 % of the lindane treated animals showed convulsions compared to 13 % in the control group. The sensitivity then declined, and 12 hours after the lindane administration the difference between the experimental group and the control group was no longer statistically significant.

As may be seen from Table 2, all the tested lindane doses, except for the lowest, elicited a significantly higher frequency of convulsions. Still, if one compares the frequency of unaffected animals in the group of mice having received 1.2 mg lindane/kg body weight with the control animals the difference is highly significant ($p < 0.0005$).

Discussion

These experiments clearly demonstrate that the convulsive threshold for pentylenetetrazol is lowered by small single oral doses of lindane in the mouse. The low lindane doses affecting the convulsive threshold and our observation of seizures occurring spontaneously in rabbits given small oral doses of the insecticide should call for a revision of the security prescriptions for handling of lindane.

In earlier experiments Herken and Klempau (1950) and Coper et al. (1951) have shown that rats given large (near lethal) oral doses of lindane are protected from the effect of convulsive doses of pentylenetetrazol, i.e. an effect quite opposite to the one described in this paper. The protective effect was found to develop a couple of days after the lindane administration and to persist for about

10 days. Experiments that are now being carried out at our laboratory, indicate that this protective effect is due to break-down products of lindane, and not to the convulsive insecticide itself.

Table 1. The effect of intravenous injections of pentylenetetrazol, 20 mg/kg body weight, on mice given single oral doses of lindane, 10 mg/kg bodyweight, at various times before the injection. The frequencies of convulsing animals in experimental and control groups are compared by means of the X^2-test.

	Time in hours between lindane administration and injection of pentylenetetrazol					
	1	2	3	6	12	24
Experimental group						
Total number of animals	22	20	30	21	21	21
Convulsing animals, %	32	65	80	43	19	9
Twitching animals, %	36	20	17	52	33	43
Unaffected animals, %	32	15	3	5	48	48
Control group						
Total number of animals	20	20	75	20	20	20
Convulsing animals, %	15	10	13	5	25	20
Twitching animals, %	15	30	19	15	30	30
Unaffected animals, %	70	60	68	80	45	50
$P <$	0.50	0.005	0.0005	0.025	0.95	0.70

Table 2. The effect of intravenous injections of pentylenetetrazol, 20 mg/kg bodyweight, on mice given single oral doses of lindane 3 hours before the injection. The frequencies of convulsing animals in experimental and control groups are compared by means of the X^2-test.

	Dose of lindane in mg/kg body weight					
	10	7.5	5	2.5	1.2	0 (control)
Total number of animals	30	23	40	25	29	75
Convulsing animals, %	80	35	30	36	17	13
Twitching animals, %	17	35	45	36	59	19
Unaffected animals, %	3	30	25	28	24	68
$P <$	0.0005	0.05	0.10	0.025	0.70	

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