

CHANGES IN DRUG METABOLISM AND
LIPOPROTEINS IN WORKERS
OCCUPATIONALLY EXPOSED TO DDT
AND LINDANE

BIRGITTA KOLMODIN-HEDMAN

Department of Occupational Health, National Board of Occupational Health, Stockholm, and Department of Clinical Pharmacology and Department of Toxicology, Karolinska Institutet, Stockholm

In twenty-six men occupationally exposed mainly to lindane and DDT antipyrine had a significantly shorter plasma half-life than in 33 control subjects. Twenty-two men exposed mainly to lindane and DDT in their occupation and 19 healthy male persons were studied with regard to their fasting serum lipid levels and to the amounts of lipids in the three ultracentrifugally separated lipoprotein families, VLDL, LDL and HDL. Eight of the exposed subjects and none of the controls had hyper-HDL (α)-lipoproteinemia. Plasma levels of lindane, p,p'-DDE and p,p'-DDT were determined with a new gas chromatographic method in forty-two spraymen exposed to lindane and in twenty-three nursery workers with a low and intermittent exposure to DDT. Controls were eleven and twenty-one respectively. The plasma lindane levels of the exposed groups differed significantly ($p < 0.001$) from the non-exposed ones. The plasma DDE and DDT values of the exposed persons did not differ from controls with only low dietary exposure to DDT. No changes in the clinical state of health could be recorded in any of the examined groups.

Induction of various drug-metabolizing enzymes by chemicals is a well-known phenomenon in experimental animals. Hepatic microsomal hydroxylating enzyme activity can be nonspecifically induced by a vast number of drugs and chlorinated insecticides (1, 2, 3). In 1963 Hart and coworkers (2) reported a shortening of hexobarbital sleeping times in rats housed in quarters which had been sprayed with chlordane. This phenomenon was for DDT paralleled by an increase of hepatic endoplasmatic reticulum and microsomal oxidative drug metabolizing enzyme activity.

One feasible way to assess the activity of liver microsomal enzymes in man is to study the plasma elimination rate of drugs which are: 1) metabolized in the liver, 2) not excreted to a great extent unchanged by the kidney, 3) not appreciably bound to plasma proteins.

I. ANTIPYRINE STUDY

This study has been published in 1969 together with *Folke Sjöquist* and *D. Azarnoff* (4).

Antipyrine is a drug suitable for the purposes mentioned above. It is rapidly absorbed, only 5 per cent is excreted unchanged in the urine, and the remainder is metabolized in the liver. The first step includes hydroxylation in the position 4 of the pyrazolone ring with subsequent conjugation (5). The plasma half-life of antipyrine in man is reported to vary between 5 to 17 hours (6) indicating marked individual differences genetically determined.

We wanted to study whether a long-term exposure to chlorinated insecticides would change the plasma half-life antipyrine.

MATERIAL AND METHODS

Subjects

Twenty-six Swedish male workers from a company handling the commercial application of insecticides voluntarily participated in this investigation. Most of them were exposed to a mixture of DDT, at that time chlordane, and lindane and some were also exposed to some organophosphates. The workers sprayed the compounds in the form of aerosols and mists, where the principle solvent was kerosene, weekly or as frequently as daily. Protective measures should have been taken, but a review of medical records and a follow-up of some patients during a work shift indicated that some exposure in the form of inhalation and skin absorption was possible. The control subjects were 15 men and 18 women mainly office personnel from the same firm. All subjects were from the same geographical area. Volunteers with a history of allergic reactions were excluded and no subject admitted any drug consumption during the 2 months preceding the investigation. They were specifically questioned concerning their use of barbiturates as well as other hypnotics and drugs which are known to affect drug metabolism.

Methods

Antipyrine was given orally in gelatin capsules in a dose of 10 or 15 mg per kilogram body weight. A blood sample for a blank reading was obtained prior to drug administration and was followed by samples drawn in heparinized tubes 3, 6, 9 and 12 hours thereafter. The blood level of antipyrine was measured according to the method of *Brodie* and associates (7).

Results

Results are given in Table 1.

The plasma half-life of antipyrine in workers exposed to chlorinated pesticides was: mean value 7.7 hours, SD 2.6 and in the controls mean value 13.7 hours, SD 7.5, median 11.5.

The half-life of antipyrine in the exposed group was significantly lower than in the control group (T level 0.01 Wilcoxon Rank Sum Test).

Table 1a
Plasma half-life of antipyrine in workers exposed to chlorinated pesticides

Initials	Sex	Dose	PT 1/2 Hours
Nn	M	10 mg/day	2.7
Nyn	M	10 mg/day	4.0
Ebg	M	10 mg/day	4.2
Gn B	M	10 mg/day	4.3
Bn O	M	10 mg/day	4.6
En	M	10 mg/day	5.0
Sn	M	10 mg/day	5.0
Bn R	M	10 mg/day	6.0
Hm n	M	10 mg/day	6.2
Gn Å	M	10 mg/day	6.8
Jr	M	10 mg/day	7.1
Pn Å	M	10 mg/day	7.3
Eld	M	10 mg/day	7.8
Ff	M	10 mg/day	8.5
Jn	M	10 mg/day	8.5
Öl	M	10 mg/day	8.8
An	M	10 mg/day	9.0
Jn PO	M	10 mg/day	9.0
Dl	M	10 mg/day	9.5
Hn	M	10 mg/day	9.5
Wn	M	10 mg/day	10.0
Kn	M	10 mg/day	10.5
Pn	M	10 mg/day	11.0
An S	M	10 mg/day	11.4
Lt	M	10 mg/day	11.5
Pn E	M	10 mg/day	11.7
		M	7.7
		SD	2.6
		Range	2.7—11.7

Table 1b
Plasma half-life of antipyrine in controls

Initials	Sex	Dose	PT 1/2 Hours
An	F	15 mg/day	5.9
Pn S	F	15 mg/day	6.0
Td	F	15 mg/day	6.8
An E	F	15 mg/day	7.2
Zm	F	15 mg/day	7.8
Ln	F	15 mg/day	10.0
Cn S	M	15 mg/day	10.3
An	F	15 mg/day	10.7
Sd	F	15 mg/day	11.0
St	F	15 mg/day	11.8
Bt	F	15 mg/day	12.5
BFT	F	15 mg/day	14.5
Sn	F	15 mg/day	16.0
Dm	M	15 mg/day	16.5
Gn G	F	15 mg/day	20.0
Ägn	F	15 mg/day	21.0
Mä	F	15 mg/day	25.5
Me	M	10 mg/day	5.2
An	F	10 mg/day	6.0
Lm	M	10 mg/day	6.2
Dn	M	10 mg/day	6.3
Smn	M	10 mg/day	6.5
Hn	M	10 mg/day	7.3
Ln	M	10 mg/day	8.2
Sg	M	10 mg/day	8.4
Nn	M	10 mg/day	9.5
Pn H	M	10 mg/day	14.5
Hn	M	10 mg/day	16.5
Adn	F	10 mg/day	16.5
Fv	M	10 mg/day	18.0
Nm	M	10 mg/day	28.0
Ln	F	10 mg/day	28.0
Wn	M	10 mg/day	35.0
	M		13.7
	Median		11.5
	SD		7.5
	Range		5.2—35.0

II. LIPOPROTEINS

The findings are published in a paper together with *L. C. Carlsson* (8).

Subjects

Twenty-two men from Stockholm, occupationally exposed to a mixture of pesticides, mainly lindane and DDT, were examined. Control subjects consisted of 38 healthy males in the age range 25—70 years. From these, blood was obtained in the fasting state and the serum lipoproteins separated ultracentrifugally and analyzed as described by *Carlsson*.

According to *Fredricksson* and *Lees* (9), changes in lipoproteins can be typed as I, IIA, IIB, III and IV.

Results

The results of the study are summarized as follows: six exposed subjects had hypertriglyceridemia (type IV pattern) and one hypercholesterolemia (type IIA). (Upper normal values 2 mmol/l of TG and > 300 mg per cent of cholesterol respectively).

Forty per cent of the subjects exposed to chlorinated pesticides and none of the controls had hyper- α -HDL lipoproteinemia. Hyper-HDL (α)-lipoproteinemia is very rare and could occur in biliary obstruction.

III. DETERMINATION OF PLASMA LEVELS OF LINDANE, DDT AND ITS ANALOGUES BY GAS CHROMATOGRAPHY

Methods

A better method than the existing ones has been developed by *Palmér, L.* and *Kolmodin-Hedman* for the analysis of small quantities of lindane in human plasma (10).

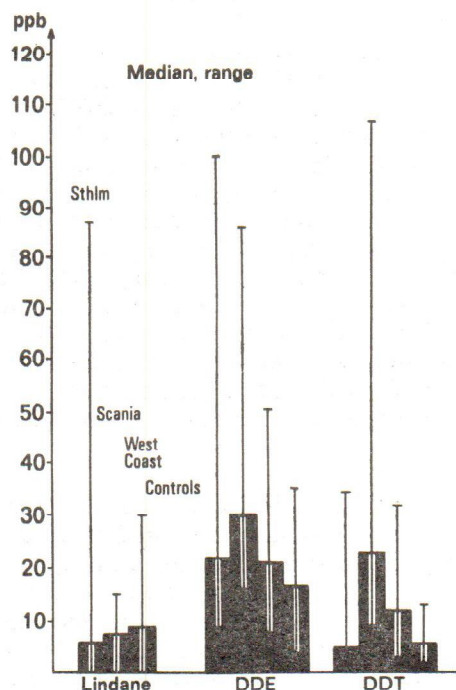


Fig. 1. Plasma levels of lindane, *p,p'*-DDE and *p,p'*-DDT expressed in ppb in occupationally exposed groups compared to controls

A practical limit of detection calculated per ml plasma was for lindane 0.3 ng, p,p'-DDE 1 ng and p,p'-DDT 3 ng. The coefficient of variance of a blood bank plasma sample containing 10 ng/ml of DDE was 6%.

DDE was quantitated and identified with a mass fragmentographic technique. The two methods agreed very well, $r = 0.99$.

Results

Plasma levels of lindane

Plasma levels in spraymen exposed to lindane are reported in the figure. The distribution of lindane levels in the Stockholm group IA, is skew but normal in the other two exposed groups. All persons had the same rated degree of exposure to lindane. Group IA had a median of 6.4 ng/ml and a range of 0–87.0 ng/ml.

In the groups coming from other geographical regions, the Southern part of Sweden and the West-coast of Sweden, the mean values of lindane were 7.5 ± 6.0 and 9.9 ± 7.5 ppb respectively. In most controls no lindane was detected.

IV. PLASMA LEVELS OF DDT AND DDE IN WORKERS EXPOSED TO DDT

Workers from pine nurseries were examined. Both sexes were represented. During the working period — spring and summer — pine and fir trees are immersed in a 1% solution of DDT in water. Only a few workers prepared the solutions. After drying the plants are set out and sometimes transplanted. Most of the staff had this occupation. The employment period varied between one month and fifteen years. Good hygienic conditions out in the fields were difficult to achieve, so that mostly dermal exposure occurred. The only analogues of DDT that were recorded in plasma were p,p'-DDE and p,p'-DDT. The DDT values are also added in the table. During exposure the mean DDE values were 15 ± 8 and DDT 10 ± 9 . Almost the same workers were examined eight months before exposure and were found to have a mean DDE-level of 16 ± 7 , DDT 10 ± 3 . Thus the intermittent low exposure to DDT was too low to cause an increase in pre-exposure levels of DDE and DDT.

Health examination

All persons investigated underwent a single health examination in which the blood pressure was measured and their body weight checked. They were carefully asked about their use of drugs. They were also carefully asked for details of their occupation, such as exposure intensity, length and so on. The health status of the Stockholm spraymen was repeatedly examined, routine laboratory tests were made and drug metabolism studied. Blood cell and plasma cholinesterase were determined. All but two men exposed to lindane were clinically healthy. These two had a lindane skin-allergy. All workers in nurseries were found healthy.

DISCUSSION

The workers occupationally exposed to lindane seemed to have plasma levels lower if compared to formulators where whole blood levels were reported (11, 12). In health examination some routine laboratory tests were also included: hemoglobin, white blood cell counts, SGPT, SGOT, bilirubin and alkaline phosphatase. Abnormal values of these parameters have been reported in literature (13, 14). All our values were normal. The only effect possibly due to lindane that could be found in examined workers were the reported changes in drug metabolism. They are suggestive of an effect on the liver microsomal enzymes of experience from animal experiments is to be extrapolated. Hexobarbital sleeping-time experiments with rats have shown that lindane levels in food down to 4 ppm regularly and occasionally down to 0.5 ppm, shorten the hexobarbital sleeping-times (15). If these data can be extrapolated from animal experiments they do not indicate a harmful effect but rather may be regarded as an adaptation of the liver to exposure to chlorinated pesticides.

We have also reported a rare change of the lipoprotein pattern. The importance of these changes is presently unknown and is object of further investigation.

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*Sažetak***PROMJENE U METABOLIZMU LIJEKOVA I LIPOPROTEINA U RADNIKA PROFESIONALNO EKSPONIRANIH DDT-ju I LINDANU**

U 26 ljudi eksponiranih pretežno lindanu i DDT-ju vrijeme zadržavanja polovične količine antipirina u plazmi bilo je znatno kraće nego u 33 kontrolne osobe.

Skupini od 22 muškarca profesionalno izloženoj lindanu i DDT-ju i kontrolnoj skupini od 19 zdravih osoba mjerena je razina serumskih lipida u gladovanju i količina lipida u tri lipoproteinske grupacije odijeljene ultracentrifugom. U osmorice od eksponiranih ispitanika nađena je hiper-HDL (α)-lipoproteinemija, a ni u jednog od kontrolnih.

Razine lindana, P,P'-DDE i P,P'-DDT u plazmi mjerene su novom kromatografskom metodom u 42 prskača eksponirana lindanu i u 23 radnika u rasadniku, izložena povremeno malim dozama DDT-ja.

Kontrolnih ispitanika bilo je 11, odnosno 21. Razina lindana u plazmi eksponiranih grupa razlikovala se signifikantno ($P < 0.001$) od one u neeksponiranih. Vrijednosti DDE i DDT-ja u plazmi izloženih osoba nisu se razlikovale od onih u kontrolnoj skupini.

Nisu nađene nikakve kliničke promjene zdravstvenog stanja u bilo kojoj od istraživanih grupa.

*Odjel za medicinu rada,
Nacionalni savjet za medicinu rada,
Odjel za kliničku farmakologiju i
Odjel za toksikologiju,
Karolinska institut, Stockholm*