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Effect of environmental factors on drug metabolism: Decreased plasma half-life of antipyrine in workers exposed to chlorinated hydrocarbon insecticides

In twenty-six men occupationally exposed to a mixture of insecticides, mainly lindane and DDT, antipyrine had a significantly shorter plasma half-life than in 33 control subjects. If the mechanism is the same as that in animals, these studies indicate that insecticides can induce microsomal drug metabolism in man.

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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, 10} In 1963, Hart and co-workers¹¹ reported a shortening of hexobarbital sleeping times in rats housed in quarters which had been sprayed with chlordane. This phenomenon was paralleled by an increase of hepatic endoplasmic reticulum and microsomal oxidative drug-metabolizing enzyme activity. Subsequently, chronic feeding of 1,1-bis (chlorophenyl) trichloroethane (DDT) and its analogues produced similar and

long-lasting effects,^{12, 13} which were obtained by use of a diet containing only 5 parts per million of DDT, a level which can be found in some human food residues.²³ Increased activity of hepatic microsomal oxidative drug metabolism in the rat was also produced by 1,1-bis (chlorophenyl) dichloroethane (DDD), perthane, kelthane, chlordane, and methoxychlor administration.¹³ In the mouse, on the other hand, DDD inhibits oxidative microsomal drug metabolism.¹³ The organophosphorus pesticides also inhibit hexobarbital metabolism in the mouse.¹²

One feasible way to assess the activity of liver microsomal enzymes in man is to study the elimination rate of drugs which are: (1) metabolized in the liver, (2) not excreted to a great extent unchanged by the kidney, and (3) not appreciably bound to plasma proteins. Antipyrine fulfills these criteria. It is rapidly absorbed, only 5 per cent is excreted unchanged in the urine,

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and the remainder is metabolized in the liver. Its metabolism includes hydroxylation in the 4 position of the pyrazolone ring with subsequent conjugation.² Recent investigations indicate that hydroxylation of the CH₃-group in the 3 position also takes place.²³ The plasma half-life of antipyrine in man is reported to vary between 5 to 17 hours,²² indicating marked individual differences.

It is known that the storage of chlorinated insecticides is lower in a general population than in occupationally exposed workers.^{8, 15, 16} To our knowledge, no data are available on the effect of exposure to insecticides on drug metabolism in man. The purpose of this investigation was to study whether long-term exposure to insecticides changes the plasma half-life of antipyrine.

Material and methods

Subjects. After a thorough discussion of the purpose and risks involved, 26 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, chlordane, and lindane (the gamma isomer of benzene hexachloride), and some were also exposed to malathion, nankor (dimethyl-2,4,5-trichlorophenyl-phosphothionate), diazinon (0,0-diethyl-0-2-isopropyl-4-methylpyrimidyl-6-thiophosphate), DDVP (dimethyl-2,2-dichlorovinylphosphate), and pentachlorophenol. The workers handled the compounds in the form of aerosols and mists (principle solvents being kerosene-like products) weekly or as frequently as daily. Protective measures should have been taken, but a review of the medical records indicated that some exposure in the form of inhalation and skin absorption was possible, as was reported by Durham⁸ and Hayes and Curley.¹⁵

The control subjects were 15 men and 18 women of Swedish descent, 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. The initial volunteers were given 15 mg. per kilogram; but when it was determined that 10 mg. per kilogram could be used satisfactorily, the dose was reduced for the remaining subjects to minimize the possibility of adverse reactions. A blood sample for a blank reading was obtained prior to the 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 associates³ except for the extraction which was done with methylene chloride. Standard curves were prepared with plasma from the blood bank at the Karolinska Hospital. Samples were analyzed in duplicate. The half-life of antipyrine in each individual was determined from the linear portion of a plot of the plasma values on semilogarithm paper. Unless otherwise noted significance was determined by the Wilcoxon Rank Sum test.^{7, 20}

Results

For the group exposed to insecticides, the half-life of antipyrine was normally distributed with a mean of 7.7, standard deviation of 2.6, a median of 7.5, and a range of 2.7 to 11.7 hours (Fig. 1). In the control group, there was a skew distribution, with a mean of 13.1, standard deviation of 7.5, a median of 11.5, and a range of 5.2 to 35.0 hours. In this group, a half-life greater than 25 hours was seen in 4 persons (Fig. 1). The half-life of antipyrine in the exposed group was significantly lower than that in the control group ($0.001 < p < 0.01$).

The half-life of antipyrine after 10 and

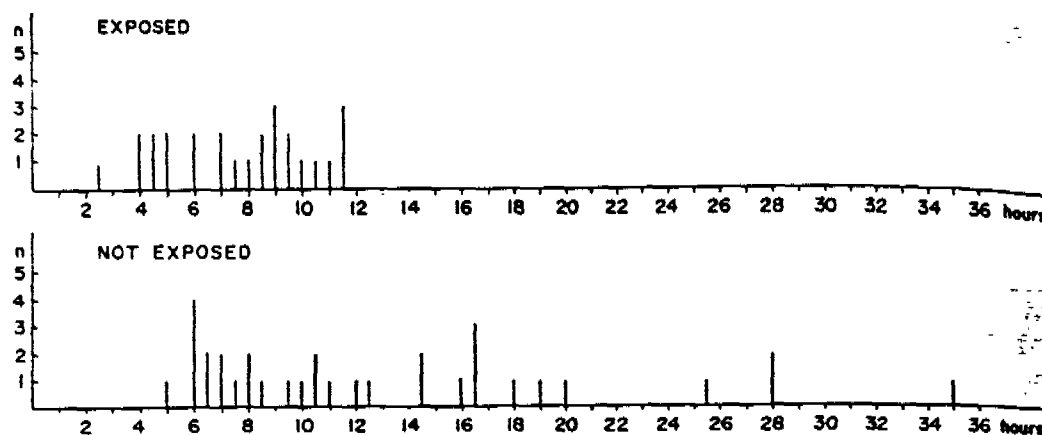


Fig. 1. Plasma half-life of antipyrine in subjects exposed to insecticides and nonexposed control subjects.

15 mg. per kilogram was not significantly different, as reported elsewhere.²² No sex difference was found. In the exposed group, no significant difference ($p = 0.4$, Student's t test) was found between smokers (7.6 ± 2.1 S.E.) and nonsmokers (7.9 ± 1.3 S.E.).

Discussion

Marked individual differences in the rate of drug metabolism in man have recently been reported for a number of compounds such as tricyclic antidepressants,^{23, 24} chlorpromazine,⁹ and phenylbutazone,^{17, 21} which are metabolized in the liver microsomes. The relative contribution of environmental versus genetic factors to these individual differences is being debated. Based on studies in twins, Vesell^{21, 22} recently suggested that the individual differences in the half-life of antipyrine and phenylbutazone were largely genetically determined.

Levi and associates¹⁷ showed that the mean was lower and the range of the half-life of phenylbutazone was smaller in patients with liver disease if they were taking various drugs thought to induce the liver microsomal enzymes. In fact, a history of previous ingestion of certain drugs was more important in determining the half-life of phenylbutazone than was se-

vere liver disease (in the place cited). In animals, it has already been shown that low exposure to low levels of certain insecticides stimulates drug metabolism. Our observations seem to be the first to indicate a similar effect of insecticides in man. The half-life of antipyrine was shorter in workers exposed to various insecticides than it was in control subjects, and the range of the half-life was considerably narrower in the exposed group. Thus, our data demonstrate that these environmental factors may play a role in regulating the rate of drug metabolism. In this context it is appropriate to call attention to the studies by Welch and associates²⁴ demonstrating the inducing effect of smoking on 3,4-benzpyrene hydroxylase activity in the human placenta and to the findings of Bledsoe and associates¹ that following treatment with o,p'-DDD, the urinary excretion of 6 β -hydroxycortisol increased in human beings probably as a result of an increased extra-adrenal hydroxylation of cortisol.⁴

The enzyme-inducing effect of insecticides on drug metabolism in animals has been shown to develop for a number of different microsomal drug-metabolic pathways.^{12, 13} It is, therefore, of value to investigate exposed subjects regarding the metabolism of other drugs, studying not only disappearance rates of parent drugs

but also the formation of various metabolites representing different pathways. Such studies are now in progress. The mixed exposure of our subjects to a variety of insecticides makes it impossible to evaluate the effect of individual compounds. Preliminary gas chromatographic analysis of chlorinated pesticides in blood from a few of the study subjects showed an increased level of lindane and DDT compared with that of the control subjects. The common denominator in all exposed workers was lindane which, in comparison with DDT and chlordane, has been meagerly investigated in animals. However, evidence in favor of an inducing effect of benzene hexachloride on drug hydroxylation has been reported in dogs¹⁶ and in rats.⁹ Experiments in progress* in this laboratory show that the metabolism of antipyrine in the isolated perfused rat liver is significantly enhanced 4 days after a single dose of lindane (60 mg. per kilogram intraperitoneally) compared with that in controls.

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