MODIFICATION OF THE EFFECTS OF CHLOROFORM ON THE RAT LIVER

BY

K. L. SCHOLLER

SUMMARY

Investigations with chloroform anaesthesia in rats pretreated with phenobarbitone indicate that the hepatotoxic action of chloroform is directly related to the activity of the microsomal drug-metabolizing enzymes. Pretreatment with disulfiram, an inhibitor of the enzymes in man and rats, completely prevents the hepatotoxicity of chloroform in rats. It would seem that the toxic effects of chloroform on the liver are due to toxic metabolites, the nature of which remains unknown. The enzymes responsible for the production of the toxins appear to be located in the centre of the hepatic acinus.

Mammals eliminate lipid-soluble drugs by biochemical transformation to water-soluble substances which are excreted in the bile and the urine. Volatile anaesthetic agents are eliminated mainly by exhalation and a small but not unimportant portion is metabolized by the microsomal enzymes which are present in the cells of the liver and kidneys (Greene, 1968). Approximately 18 per cent of the halothane vapour inhaled during anaesthesia is metabolized in man to the nontoxic trifluoroacetate, inorganic bromide and chloride (Rehder et al., 1967). Chloroform is metabolized in similar amounts to carbon dioxide and inorganic chloride by the above-mentioned enzymes (van Dyke, Chenoweth and van Poznak, 1964).

Opinions differ as to the cause of the hepatotoxicity of chloroform. Vasoconstrictive restriction of the blood flow in the liver lobules (Calvert and Brody, 1960) or toxic metabolites (Kochmann, 1923; Scholler, 1968; van Dyke, 1969) have been cited as causes. The purpose of the present study was to determine the relationship between microsomal enzymatic activity and the appearance of hepatic necrosis in rats following exposure to chloroform vapour.

METHOD AND RESULTS

In order to stimulate the activity of the microsomal metabolizing enzymes Sprague-Dawley rats were given phenobarbitone 60 mg/kg by intramuscular injection daily for 11 days. On the 13th day 9 rats were anaesthetized with chloroform for 30 minutes (1 vol. per cent in oxygen); 7 control animals received phenobarbitone only; 5 rats were treated with chloroform only. Twenty-four hours after the termination of the experiment the activity of the serum transaminases was determined.

Damage to liver cells causes an escape of liver cell enzymes into the circulation. The rise in activity of liver cell enzymes in serum, particularly transaminases, is closely related to the degree of liver damage. Measurement of the SGP-transaminase activity is a particularly sensitive and specific test of liver damage. As the transaminases are approximately evenly distributed in the liver cells in the whole lobule, they are also a sensitive indicator of the extent of central necrosis.

The breadth of the necrotic central zone in the liver lobule was measured microscopically by an ocular micrometer in two diameters which cross each other at right-angles. The average breadth was calculated for the two groups, one group having received chloroform alone and the other having received phenobarbitone and chloroform. The results are shown in figure 1. The statistical comparison (t-test) yielded a difference of high significance (P<0.01).

Dr. med. K. L. SCHOLLER, Inst. fur Anaesthesiologie der Univ.-Kliniken, 78 Freiburg, Hugstetterstrasse 55, Germany.
Disulfiram* (tetraethylthiuram disulphide) 500 mg/kg, an inhibitor of microsomal drug-metabolizing enzymes (Honjo and Netter, 1969), was given via a gastric tube to each of 6 rats 90 minutes before chloroform anaesthesia which lasted for 2½ hours in each instance. Neither an increase of serum transaminase activity nor necrosis nor fatty infiltration of hepatic cells was recorded, compared with rats which had received 2½ hours chloroform anaesthesia without disulfiram and which suffered more severe liver necrosis than the group which had received chloroform for ½ hour.

**COMMENT**

The increase of activity of microsomal enzymes which split chloroform can be induced by phenobarbitone or by certain insecticides such as DDT (McLean and Witschi, 1966). The higher activity of the enzymes is associated with a statistically significant increase in the hepatotoxic effect of chloroform. Disulfiram, which inhibits the breakdown of lipid-soluble drugs, is able to suppress the toxicity of chloroform completely, when the appropriate dose is given before the administration of chloroform. These findings suggest that...
the toxic metabolites of chloroform damage the liver cells, especially in the centre of the acinus.

In the last year several reaction products of the free radical \( \cdot \text{CCl}_3 \) of carbon tetrachloride with unsaturated fatty acids in the phospholipid fraction of liver cells have been discovered (Gordis, 1969). There are several reasons for assuming that the toxic metabolites of chloroform are of a similar nature, but lower in quantity.

An unchanged activity of serum transaminases 24 hours after a chloroform anaesthesia has often been given as proof of non-hepatotoxicity of chloroform in man. In order to detect the signs of liver damage from chloroform anaesthesia in man it is advisable to study the activity of the serum transaminases up to the third and fourth day after anaesthesia (Scholler, Kohnlein and Carsjens, 1965) in contrast to rodents.

REFERENCES


Greene, N. M. (1968). The metabolism of drugs employed in anaesthesia, Part II. Anesthesiology, 29, 327.

