Effect of Phenobarbitone and Indoxyl Sulphate on Biliary Excretion of Foreign Organic Compounds during Administration of Carbon Tetrachloride

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Metabolism of carbon tetrachloride is essential for its toxic effect on intracellular components of the hepatocytes (Butler, 1961; Recknagel, 1967). Carbon tetrachloride decreases the biliary excretion of foreign organic compounds of high molecular weight (Barakat & Abou-El-Markarem, 1973). Whether metabolism of carbon tetrachloride is also essential for this effect, will be discussed here.

Various doses of carbon tetrachloride (50-1500 mg/kg body wt. dissolved in 2.5 ml of olive oil) were administered orally or intraperitoneally to female Wistar albino rats. Serum bilirubin concentration did not increase after a single oral dose of carbon tetrachloride. The rats developed jaundice (serum bilirubin <3 mg/100 ml) after the third oral dose. Serum glutamic-pyruvic transaminase (EC 2.6.1.2) and glutamic-oxaloacetic transaminase (EC 2.6.1.1) reached a maximum at doses of 250 mg of carbon tetrachloride/kg body wt. Increasing the dose of carbon tetrachloride, repeated administration or

![Graph](image)

**Fig. 1. Biliary excretion of various doses of phenolphthalein disulphate during administration of carbon tetrachloride**

Phenolphthalein disulphate was administrated intravenously to rats as an aqueous solution of the tripotassium salt. Treatment of rats was as in Table 1. ○, Control rats; ●, rats after oral administration of carbon tetrachloride; □, rats pretreated with phenobarbitone intraperitoneally and carbon tetrachloride orally; △, rats pretreated with indoxyl sulphate intraperitoneally and carbon tetrachloride orally; ▲, rats pretreated with indoxyl sulphate and carbon tetrachloride intraperitoneally.
Table 1. Biliary excretion of foreign organic compounds during administration of carbon tetrachloride in rats pretreated with phenobarbitone or indoxyl sulphate

Results are the mean of five or more experiments ± S.D. Sodium phenobarbitone (70 mg/kg given twice daily for three successive days intraperitoneally before administration of carbon tetrachloride and during its administration) induction was measured. Indoxyl sulphate (20 mg/kg body wt.) was given intraperitoneally the day before and with carbon tetrachloride. The doses of the test compounds were 50 mg/kg body wt. dissolved in water and given intravenously.

<table>
<thead>
<tr>
<th>Dose of carbon tetrachloride (mg/kg)</th>
<th>Test compound</th>
<th>4-Aminophenyl glucuronide</th>
<th>Phenolphthalein disulphate</th>
<th>Phenolphthalein glucuronide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td></td>
<td>0.2 ± 0.1</td>
<td>56.6 ± 8.7</td>
<td>62.4 ± 9.4</td>
</tr>
<tr>
<td>100 (orally)</td>
<td></td>
<td>0.3 ± 0.1</td>
<td>20.4 ± 5.2</td>
<td>22.6 ± 4.8</td>
</tr>
<tr>
<td>+phenobarbitone</td>
<td></td>
<td>0.3 ± 0.1</td>
<td>18.2 ± 6.4</td>
<td>24.1 ± 6.4</td>
</tr>
<tr>
<td>+indoxyl sulphate</td>
<td></td>
<td>0.2 ± 0.1</td>
<td>64.2 ± 10.7</td>
<td>59.0 ± 8.6</td>
</tr>
<tr>
<td>100 (intraperitoneally)</td>
<td></td>
<td>0.3 ± 0.1</td>
<td>23.1 ± 4.3</td>
<td>19.4 ± 7.2</td>
</tr>
<tr>
<td>+phenobarbitone</td>
<td></td>
<td>0.2 ± 0.1</td>
<td>21.4 ± 2.4</td>
<td>20.0 ± 4.8</td>
</tr>
<tr>
<td>+indoxyl sulphate</td>
<td></td>
<td>0.2 ± 0.1</td>
<td>37.2 ± 7.4</td>
<td>32.6 ± 3.2</td>
</tr>
</tbody>
</table>
intraperitoneal administration caused no further change in the activity of the serum transaminases (Korsrud et al., 1972). On the other hand, the effect of carbon tetrachloride on biliary excretion of phenolphthalein disulphate and phenolphthalein glucuronide was dose-dependent up to 1250 mg of carbon tetrachloride/kg body wt.

Phenobarbitone pretreatment did not increase the effect of carbon tetrachloride on the biliary excretion of phenolphthalein conjugates (Table 1).

Indoxyl sulphate (an alkylating agent) partially protected the excretory function of the liver from the toxic effect of carbon tetrachloride when administered intraperitoneally and completely when given orally. Serum transaminases activities in blood were increased. The maximum dose of phenolphthalein disulphate excreted in bile of rats pretreated with indoxyl sulphate and carbon tetrachloride was similar to that of the control. Phenobarbitone did not improve or decrease the biliary transport maximum of phenolphthalein disulphate after oral or intraperitoneal administration of carbon tetrachloride (Fig. 1).

Phenobarbitone improved the rat liver capacity to concentrate phenolphthalein disulphate. The concentration in bile was not increased. The concentrative capacity of the hepatocytes to bile was improved markedly in rats after pretreatment with indoxyl sulphate.

Phenobarbitone increases the rate of metabolism of carbon tetrachloride (Garner & McLean, 1969), yet it did not augment the toxic effect of carbon tetrachloride on the excretory mechanism of rat liver. Indoxyl sulphate decreased the rate of metabolism of [14C]carbon tetrachloride to 14CO2 in liver slices. The protecting effect was mainly after oral administration of carbon tetrachloride, as was seen with compound SKF 525A (Marchand, 1970). With [14C]carbon tetrachloride, the concentration of the radioactivity in the liver was less in rats pretreated with indoxyl sulphate than in controls.

It seems that the effect of carbon tetrachloride on the excretory function rat of liver may not be related to its metabolism.

We are grateful to Professor H. Remmer for fruitful discussions.


NADPH–Cytochrome c Reductase, Cytochrome P-450 and NADPH-Linked Lipid Peroxidation in Microsomal Fractions Obtained from Rat Tissues

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Microsomal suspensions obtained from rat liver, and to a lesser extent from kidney, contain an active NADPH-cytochrome P-450 electron-transport chain that has an important function in the metabolism of a wide variety of foreign compounds (see Briggs & Briggs, 1974). Microsomal suspensions prepared from other rat tissues, such as lung, adrenal and testis, have been reported (see Orrenius & Ernster, 1974) to contain detectable quantities of cytochrome P-450, but the contribution of these tissues to the total body metabolism of a foreign compound is small compared with that of the liver in the rat (Knecht, 1966). Nevertheless, although such metabolism may be