Lipid abnormalities in workers exposed to dioxin

J V MARTIN

From Oldham and District General Hospital, Oldham OL1 2JH, UK

ABSTRACT Ten years after an incident in which workers were exposed to tetrachlorodibenzodioxin (TCDD) a controlled biochemical study showed statistically significant increases in the serum cholesterol and triglyceride concentrations of workers both with and without chloracne. Urinary excretion of D-glucaric acid was significantly higher for all workers. Tetrachlorodibenzodioxin (TCDD) is a potent multisystem toxin with high acute toxicity, the LD₅₀ for several species being of the order of 0·1 mg/kg bodyweight. Other toxic effects include chloracne, impaired liver function, carcinogenesis, lipid abnormalities, porphyria, peripheral neuropathy, and psychiatric disturbances.

It has been suggested that some of the toxic effects of TCDD may be linked to its enzyme inducing action. In epidemiological research on subjects exposed to TCDD life style factors such as social class, alcohol intake, dietary and smoking habits, and drug therapy could have a confounding effect because of differences between subjects and controls in the extent of enzyme induction due to agents other than TCDD. In this study, therefore, the subject and control populations were matched for age, social class, alcohol intake, smoking habits, height/weight ratios, and drug therapy.

Subjects with and without chloracne who had been exposed to TCDD were tested as, although the presence of chloracne is a good indicator of exposure to TCDD, evidence from a study of workers exposed to a different chloracneugen shows that it does not necessarily follow that its absence in an individual exposed to TCDD precludes the possibility of other toxic manifestations.

Methods

Subjects were asked to fast for 10 hours (overnight) and a venepuncture sample of blood was obtained at 9 30 am for the following biochemical tests: alkaline phosphatase, alanine and aspartate aminotransferase, bilirubin, protein corrected calcium, total and HDL cholesterol, triglyceride and gammaglutamyl transferase (GGT). D-glucaric acid/creatinine ratios (DGA) were measured on a sample of urine taken at the same time. All estimates were carried out using standard methodology in two NHS laboratories with some of the analyses being carried out in both laboratories.

Results

The table shows the means and range of values, plus the laboratory’s normal range for those of the tests where there were differences between the subjects and controls. Mean cholesterol and triglyceride are significantly higher in groups B and C than in the controls. The parameters of enzyme induction, GGT and DGA, were raised in both groups of subjects but only in respect of DGA were they significantly higher than the controls. Serum bilirubin and protein corrected calcium concentrations were lower in both groups of subjects, although only for the latter did they differ significantly from the controls. The correlation coefficient (r) for the relationship between GGT and triglyceride in the subjects exposed to TCDD was +0·44, p < 0·001.

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Biochemistry: mean values

<table>
<thead>
<tr>
<th>Test (units)</th>
<th>Laboratory normal range</th>
<th>Controls mean (and range) (n = 126)</th>
<th>Subjects without chloracne mean (and range) (n = 53)</th>
<th>Subjects with chloracne mean (and range) (n = 39)</th>
<th>All subjects mean (and range) (n = 92)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholesterol (mmol/l)</td>
<td>3-5-7-8</td>
<td>5-6</td>
<td>6-14*</td>
<td>6-02**</td>
<td>6-09***</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(2-8-8-3)</td>
<td>(4-5-8-6)</td>
<td>(2-9-8-1)</td>
<td>(2-9-8-6)</td>
</tr>
<tr>
<td>Triglyceride (mmol/l)</td>
<td>Up to 2-2</td>
<td>1-41</td>
<td>1-90*</td>
<td>1-97***</td>
<td>1-93***</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(0-3-3-2)</td>
<td>(0-4-4-6)</td>
<td>(0-4-4-0)</td>
<td>(0-4-4-6)</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/l)</td>
<td>1-25</td>
<td>1-23</td>
<td>1-19</td>
<td>1-22</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(0-8-2-02)</td>
<td>(0-65-1-22)</td>
<td>(0-89-1-88)</td>
<td></td>
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<tr>
<td>Gamma-glutamyl transferase</td>
<td>Up to 35</td>
<td>32</td>
<td>36</td>
<td>40</td>
<td>37-4</td>
</tr>
<tr>
<td>(U/L at 37°C)</td>
<td></td>
<td>(11-90)</td>
<td>(10-120)</td>
<td>(14-91)</td>
<td>(10-120)</td>
</tr>
<tr>
<td>D-glucaric acid (ratio)</td>
<td>Up to 3-5</td>
<td>2-09</td>
<td>2-09</td>
<td>2-09**</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(0-8-8-3)</td>
<td>(0-7-7-6)</td>
<td>(0-7-7-9)</td>
<td></td>
</tr>
<tr>
<td>Bilirubin (μmol/l)</td>
<td>10-47</td>
<td>10-1</td>
<td>9-5</td>
<td>9-84</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(5-23)</td>
<td>(4-23)</td>
<td>(4-23)</td>
<td></td>
</tr>
<tr>
<td>Protein corrected calcium</td>
<td>2-33</td>
<td>2-307</td>
<td>2-282***</td>
<td>2-285***</td>
<td></td>
</tr>
<tr>
<td>(mmol/l)</td>
<td></td>
<td>(2-12-2-46)</td>
<td>(2-14-2-47)</td>
<td>(2-10-2-61)</td>
<td>(2-10-2-61)</td>
</tr>
</tbody>
</table>

*p < 0.005; **p < 0.05; ***p < 0.001; ****p < 0.001. Level of significance of the difference between the means of subjects and controls.

Discussion

This work confirms previous findings of a relationship between human TCDD exposure and abnormalities of all three lipid fractions estimated.8-13 Lipid abnormalities in experimental animals exposed to TCDD are also well recognised.14-16

The consensus of opinion is that raised total cholesterol and low HDL cholesterol concentrations probably confer an increased risk of ischaemic vascular disease.17 A recent study has also shown a convincing relationship between raised triglycerides and coronary atheroma.18 Consistently, two small human studies7,13 and one uncontrolled study (A P Redgrave, personal communication) have suggested a link between exposure to TCDD and ischaemic vascular disease, and there have been two case reports of premature coronary atheroma, diagnosed clinically and by angiography in sprayers of the herbicide 2, 4, 5-T which is contaminated with varying amounts of TCDD.19 Intravascular thrombosis has also occurred in rats exposed to TCDD.20 The failure to show an increased incidence of ischaemic vascular disease in two studies of workers exposed to TCDD4,31 may have been due to failure to include an adequate proportion of all affected employees in the first study (A P Redgrave and J V Martin, personal observations) and failure to include subjects without chloracne in the second.

The significant positive correlation between GGT and triglyceride, the significantly lower serum calcium concentrations, and the significantly higher DGA concentrations support the hypothesis that enzyme induction by the TCDD could be the explanation for the abnormal lipid concentrations. The duration of the abnormalities in years rather than months is not an argument against this as has been suggested,9 because raised DGA concentrations were found up to three years later in the TCDD exposed Seveso population.22 Whatever the mechanism for the lipid abnormalities, they have been found to persist for 10 years in another controlled study of workers exposed to TCDD.23

This comparison of TCDD exposed workers with a control group matched for social class and known relevant variables confirms other workers’ findings by various experimental approaches of TCDD induced lipid abnormalities and their possible clinical consequences.

References


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