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SHORT COMMUNICATION

Parathion and Diisopropylfluorophosphate (DFP) Toxicity in Partially Hepatectomized Rats

Parathion and Diisopropylfluorophosphate (DFP) Toxicity in Partially Hepatectomized Rats. JACOBSEN, P. L., SPEAR, R. C. and WEI, E. (1973), *Toxicol. Appl. Pharmacol.* **26**, 314–317 (1973). The toxic effects of parathion and DFP in male rats either increased or remained unchanged after partial hepatectomy. LD_{50} values and blood cholinesterase activities were used as indices of toxicity. These results suggest that parathion toxicity is most likely not due to hepatic conversion of parathion to paraoxon.

Although the liver is generally considered a detoxifying organ (Williams, 1959), the biotransformation of some chemicals by liver enzymes results in compounds with increased biological activity (Shuster, 1964; Conney, 1967). Diggle and Gage (1951a) first showed that the in vivo inhibition of cholinesterase by parathion is dependent on the metabolic conversion of parathion to paraoxon. It is not clear, however, if liver enzymes, which have the highest capacity for converting parathion to paraoxon, generate the paraoxon molecules responsible for systemic poisoning. Alary and Brodeur (1969, 1970) examined in detail the stimulation of parathion metabolism by phenobarbital in order to explain the apparently paradoxical protective effect afforded by phenobarbital against parathion toxicity. Neal (1972) has recently suggested that extrahepatic conversion of phosphothionate insecticides to the corresponding toxic phosphates may account for the toxicity of these compounds. Evidence cited in favor of Neal's viewpoint was the observation of Diggle and Gage (1951b) that total hepatectomy did not make rats less sensitive to parathion. Since the hepatectomy experiments were not reported in detail, we decided to further examine the role of the liver in parathion toxicity by studying parathion and DFP toxicity in partially hepatectomized rats.

METHODS

Male Sprague–Dawley rats obtained from Horton Laboratories, Oakland, CA (180 ± 15 g) were used throughout these experiments. Animals were randomly assigned to different treatment procedures. Partial hepatectomies were performed according to the procedure described by Lambert (1965). Rats were anesthetized with ether; after laparotomy the median and left liver lobes were brought to the exterior and ligated at the base of the hilum. The lobes were then excised and the peritoneal incision sutured with thread and closed with wound clips. This procedure removes approximately 70% of the liver. In sham-operated animals the liver was brought to the exterior and then returned to the peritoneal cavity without ligation, otherwise anesthetic and surgical procedures were identical to that of hepatectomized animals. No postoperative mortality, attributable

to partial removal of the liver, was encountered during the time period of the experiment.

Test compounds were administered po with a ball-tipped 7.5-cm, 16-gauge stainless-steel needle, 22–24 hr after partial hepatectomy or sham-operation. Food was removed from cages 12 hr prior to drug administration in order to minimize possible variability in gastrointestinal absorption. The short period between surgical stress and experimentation was necessitated by the rapid rate of liver regeneration in the rat (Lambert, 1965).

The 36-hr LD_{50} values for DFP or parathion in partially hepatectomized or sham-operated rats were calculated according to the method of Weil (1952). The doses for DFP in hepatectomized animals were 1.8, 2.5, 3.5, and 4.9 mg/kg and for sham-operated rats, 3.6, 5.1, 7.1, and 10 mg/kg. The doses for parathion in hepatectomized rats were 0.89, 1.3, 2.0, and 3.0 mg/kg and in sham-operated animals, 5.0, 7.5, 11.25, and 16.9 mg/kg. At least four animals were used at each dose level. The vehicle for parathion (Aldrich Chemical Co., Milwaukee, WI) and DFP (Monsanto Commercial Products Co., St. Louis, MO) was propylene glycol (80%) – ethanol (20%) v/v. The parathion used in these experiments was at least 99.8% pure when analyzed by gas–liquid chromatography.

For blood cholinesterase measurements, animals received 1 mg/kg po of either DFP or parathion and 30-μl blood samples were then collected from the orbital sinus with heparinized capillary tubes at 0, 1, 2.5, and 4 hr. Animals were lightly anesthetized with ether during blood sampling. Whole-blood cholinesterase activity was determined by the method of Voss and Sachsse (1970). Enzyme activities were expressed in absorbance units.

RESULTS AND DISCUSSION

The LD_{50} values for parathion and DFP in sham-operated rats were 7.5(5.9–9.1) and, 7.6(6.4–8.8) mg/kg, respectively. Partial hepatectomy markedly increased the lethal effects of both substances. After hepatectomy the LD_{50} values for parathion and DFP were 1.5(0.2–2.8) and 3.0(1.7–4.3) mg/kg, respectively. Since DFP is a direct inhibitor of cholinesterase, the increased susceptibility of hepatectomized animals to the lethal effects of parathion and DFP may have been due to a nonspecific debilitating effect of liver removal. Therefore, to examine a more specific effect of organophosphate toxicity, we measured the effects of DFP and parathion on blood cholinesterase activity.

Cholinesterase activity in animals receiving only the propylene glycol–ethanol vehicle was not significantly affected by the procedures used for blood sampling (Fig. 1). At a dose which was not lethal to any animal in the 4-hr experimental period, both parathion and DFP decreased blood cholinesterase activity in sham-operated and partially hepatectomized rats (Fig. 1). Partial hepatectomy did not affect the depression of cholinesterase activity produced by parathion, but appeared to enhance the effect of DFP.

Although complex physiological and biochemical alterations are produced by partial hepatectomy the results clearly indicate that partial removal of the liver does not attenuate the lethal effects or the in vivo inhibition of cholinesterase produced by parathion or DFP. These results confirm the protective function of the liver against parathion toxicity and further support Neal's (1972) suggestion that extrahepatic metabolism of parathion to paraoxon may account for the toxicity of parathion.

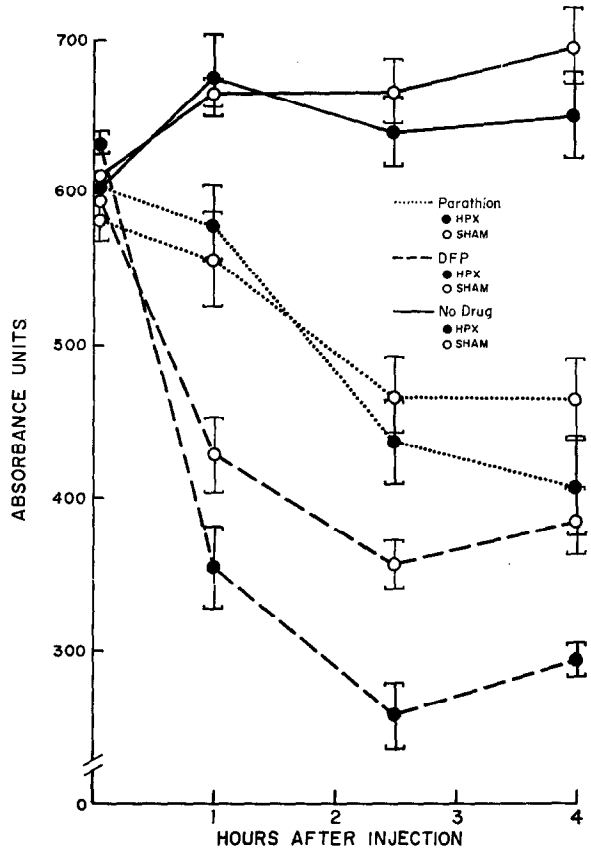

FIG. 1. Blood cholinesterase activity after administration of 1 mg/kg po of parathion, DFP or vehicle to sham-operated (SHAM) or partially hepatectomized (HPX) rats. Values represent the mean ± SE, eight animals were used for each group. The DFP-HPX group has significantly ($p < 0.05$, t test) lower cholinesterase activity at 1, 2.5, and 3 hr after DFP administration when compared to DFP-SHAM.

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