Thesis Title Toxicological effects of Monocrotophos on specific activities of acetylcholinesterase in different brain regions and the development of tolerance in rat

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ABSTRACT

The 50 percent lethal dose(LD_{50}) and the dose for 50 percent reduction (ED_{50}) of the specific activity of enzyme acetylcholinesterase (AChE) for a widely used organophosphate(OP) insecticide, Monocrotophos(MCP) were investigated in the rat after 1 hr of intraperitoneal injection. The effect of MCP on reduction of specific activity of AChE in all three brain areas were found to be dose-dependent and well correlated in the cerebral cortex, hippocampus and striatum (correlation coefficient values between 0.986 to 0.997). In this study, the ED_{50} values for reduction of specific activity of AChE in the cerebral cortex, hippocampus and striatum were found to be approximately 0.22 mg/kg, 0.27 mg/kg and 0.36 mg/kg, respectively. The LD_{50} value was about 5.1 mg/kg.

The present data indicated that there was comparatively no specific efficacy and/or affinity of MCP to these brain regions. There was no correlation between the LD_{50} and ED_{50} values. The present data was different from other previous investigation which showed that ED_{50} value for inhibition of blood cholinesterase(ChE) was found to be roughly agreed with LD_{50} value. The time course of the inhibitory effect of MCP on specific activity of AChE in the cerebral cortex, hippocampus and striatum was determined at 1, 4 and 24 hrs after intraperitoneal injection of MCP (4 mg/kg). After 1 hr of injection specific activity of AChE dropped to approximately 20 percent of control and did not recover markedly during the first 4 hrs, but returned significantly to approximately 70 percent of control after 24 hrs($P<0.001$). The patterns of changes in specific activity of AChE were consistent in all three brain regions studied. The experimental evidence indicated that the effect of a single sublethal dose of MCP on specific activity of AChE is rapidly reversible within 24 or 48 hrs.

In another study, the tolerant phenomenon after repeated exposure to MCP was studied in the rats by measuring several parameters including mean body weight (MBW), abnormal cholinergic signs such as convulsion and tremor, mortality and specific activity of AChE in the cerebral cortex, hippocampus and striatum of brain regions. Rats were daily injected intraperitoneally with either MCP(3 mg/kg/5 ml) or distilled water(5 ml/kg) for

14 days duration. Body weight was recorded before each injection. MBW of treated rats declined significantly ($P<0.025$) after 2 days of injections, became stabilized from day 7 to day 10 and later increased with the same rate of growth compared to the control although treated rats did not reach body weight attained by control group. Tremor and convulsion were most severe during the first 5 days and dropped to below 50 percent of the population after 1 week. After 10 days, no animal showed any significant tremor and convulsion. Mortality rates as shown by the percentage of death rats in the population showed two prominent peaks. The first peak of 20 percent of population occured after 2 days of injection of MCP, and the seccond peak of 14 percent on day 5. After 8 days there was no more death in the treated group. None of the animals in the control group died or had abnormal cholinergic signs. Twenty-four hrs after 1, 3, 7 and 14 injections, rat were decapitated and specific activity of AChE in the cerebral cortex, hippocampus and striatum was measured. Specific activity of enzyme AChE returned to about 70 percent of the control group($P<0.001$) after 1 day but dropped significantly ($P<0.001$) at day 3 and by day 7 to 45-60 percent and 30-40 percent of control, respectively, then became stabilized through out the rest of the experiment. The reduction of AChE activity in all brain regions studied at all time point were similar in the patterns of change. The experimental evidence suggested that tolerance develop in rat after

repeated exposure to MCP and this probably was not due to metabolic enzyme induction. We propose that the tolerance may be due to an alteration in de novo synthesis of AChE and an adaptation or alteration of synaptic receptor plasticity of either or both cholinergic and GABA system which play a part in the compensatory process to counteract the excessive cholinergic activity produced by MCP.

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