THE CARDIOVASCULAR TOXICITY OF CHLORDIMEFORM:

A LOCAL ANESTHETIC-LIKE ACTION

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INTRODUCTION

Chlordimeform (CDM) is a formamidine pesticide with interesting and unusual biological activities (Hollingworth, 1976). It is moderately toxic to mammals (mouse oral LD$_{50}=195$–310 mg/kg; Hollingworth, 1976). It has little action on cholinergic transmission in insects or mammals (Dittrich, 1966; Beeman and Matsumura, 1973), although a decrease in acetyl choline receptor sensitivity has been observed in frog muscle following large doses of CDM (Wang et al., 1975; Watanabe et al., 1975). CDM and related compounds inhibit monoamine oxidase in rat and mouse liver (Beeman and Matsumura, 1973; Aziz and Knowles, 1973) and uncouple oxidative phosphorylation and electron transport in rat liver mitochondria (Abo-Khatwa and Hollingworth, 1974). Although each of these authors suggested that such actions could be involved in acute toxicity, no one has satisfactorily related these biological actions to toxicity. Furthermore, certain poisoning symptoms such as the rapid onset of tremors and convulsions could not be explained readily by either of these biochemical sites of action (Neumann and Voss, 1977; Lund et al., 1977). Thus the cause of death and the physiological mechanisms underlying some symptoms remain unknown.

Beeman and Matsumura (1974) showed that 200 mg/kg CDM given i.p. decreased the mean arterial blood pressure in the rabbit, but they did not further investigate the mechanism of the hypotensive action. The purpose of this investigation was to study the action of CDM on the mammalian cardiovascular system and contribution of such actions to the lethal effects of CDM.
METHODS

Arterial blood pressure and heart rate were monitored in 7-12 kg dogs anesthetized with pentobarbital. Right ventricular contractile force was measured with a strain gauge sewn onto the heart while the animals were artificially resired. Peripheral vascular resistance was measured by perfusing a hind limb at a constant flow rate (27 ml/minute) with blood taken from the femoral artery and monitoring changes in the perfusion pressure. Drugs were administered via the cephalic vein or the femoral artery (hind limb perfusion experiments only).

RESULTS AND DISCUSSION

Chlordimeform at doses of 1-30 mg/kg i.v. caused initial decreases in mean arterial blood pressure and cardiac contractility within one minute, followed by secondary increases above predrug levels (Figure 1). These parameters returned to control levels within one hour. There was relatively little effect on the heart rate. Hyperventilation, tremors and occasional clonic convulsions were associated with the transition from the depressor to the pressor responses in lightly anesthetized dogs.

Fig. 1. Response of heart rate, cardiac contractility and blood pressure to 30 mg/kg CDM i.v. Arbit. units=Arbitrary units.