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THE ROLE OF MONAMINE OXIDASE INHIBITION IN THE ACUTE TOXICITY OF CHLORDIMEFORM

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16. Abstract

This paper presents data from experiments on male rats performed to determine whether drugs which interfere with central amine mechanisms would decrease the lethality of the acaricide chlordimeform (and thus be of potential value as antidotes for accidental poisoning) or increase chlordimeform lethality (and thus should be avoided by aerial applicators and others in contact with it). Neither reducing serotonin synthesis with p-chlorophenylalanine, reducing norepinephrine synthesis with DL-α-methyl-p-tyrosine nor depleting both amines with reserpine affected the lethality of chlordimeform. Likewise, blocking α-adrenergic receptors with phentolamine or the serotonergic receptors with methysergide, or both, did not influence chlordimeform lethality. The adrenergic agonist drug phenylephrine also did not affect chlordimeform lethality. Thus, the results indicate that: (1) monamine oxidase inhibition does not play a major role in acute chlordimeform lethality; (2) none of the drugs tested shows promise in the treatment of chlordimeform poisoning, and (3) aerial applicators or others would appear to incur little or no extra risk should they be taking any of the above drugs during potential exposure to chlordimeform.

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reserpine	phenylephrine	
methysergide	p-chlorphenylalanine	
phentolamine		

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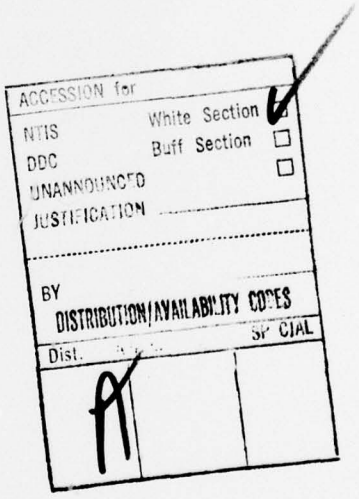


THE ROLE OF MONAMINE OXIDASE INHIBITION IN THE ACUTE TOXICITY OF CHLORDIMEFORM

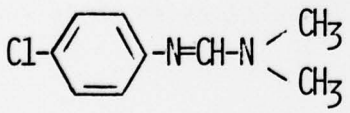
I. Introduction.

Chlordimeform, also known as Galecron^R, Fundal^R, or chlorphenamidine, is a specific acaricide, highly effective in the control of ticks and mites, members of the taxonomic order Acarina, responsible for substantial agricultural losses.

Our decision to study certain aspects of the toxicology of chlordimeform was based on two principal considerations. One of these was the fact that chlordimeform possesses many favorable properties as a pesticide, from which it could be predicted that its use would increase, with increased opportunity for contact by agricultural pilots and their support personnel. Secondly, it represents a new class of pesticides chemically, with no close resemblance to any of the hundreds of previously used pesticides, and the mechanisms of its toxic actions have not been fully determined.

As a pesticide, chlordimeform has many desirable properties. It is effective against ova, larvae and adult forms as demonstrated by Dittrich (1966) and Dittrich and Loncarevic (1971). Ehrhardt and Knowles (1970) and Bull (1973) found that it penetrates leaves rapidly at the site of contact and is translocated to other parts of the plant. It has an appreciable vapor pressure, and Bull (1973) found that it disappears from the surface of foliage within a few hours. Thus it kills pests by three routes of attack: direct contact or ingestion of the sprayed chemical, contact in the vapor phase, and ingestion of the permeated plant substance. It is effective against organisms which have become resistant to organophosphates, carbamates and other types of pesticides.

Given these advantages, and because it was recommended for use on large acreage crops such as cotton, its use was increasing. In September 1976, after these studies were completed, it was voluntarily withdrawn from the market by its manufacturers because it may cause malignant tumors in a certain strain of laboratory mice. If further study proves it safe, however, it could again be released for further use. It is a formamidine (structure below).



The metabolism, pharmacologic effects and mode of toxicity of chlordimeform have been the subject of several investigations. Its metabolism has been investigated in apple seedlings by Sen Gupta and Knowles (1969), grapefruit seedlings by Ehrhardt and Knowles (1970), cotton plants by Bull (1973),

microbes by Johnson and Knowles (1970), houseflies by Knowles and Shrivastava (1973), ticks by Knowles and Roulston (1972, 1973), rats by Ahmad and Knowles (1971) and Knowles and Sen Gupta (1970), dogs and goats by Sen Gupta and Knowles (1970) and in human embryonic lung cell cultures by Lin and coworkers in 1975.

It was reported not to inhibit cholinesterases by Dittrich (1966) and by Beeman and Matsumura (1973), and to cause no signs of cholinergic stimulation by Beeman and Matsumura (1973). Thus it does not interfere with the parasympathetic nervous system as do many insecticides. Abo-Khatwa and Hollingworth reported an interference with energy metabolism by the uncoupling of oxidative phosphorylation in the German cockroach (Blattela germanica) (1972) and the rat (1973), and postulated that this contributed to chlordimeform toxicity.

More recently it has been postulated that an interference with the sympathetic nervous system contributes to the toxicity of chlordimeform. This seems to be a unique action among insecticides. Chlordimeform inhibits the enzyme, monoamine oxidase (MAO), which is involved in the inactivation of the sympathetic neurotransmitter norepinephrine (NE) as well as other catecholamines and serotonin both in brain and peripheral tissues. Inhibition of mammalian (rat liver) MAO has been reported by Beeman and Matsumura (1973) and by Aziz and Knowles (1973) and of invertebrate (cockroach head) MAO by Beeman and Matsumura in 1974. Beeman and Matsumura reported that acute, toxic doses increase the concentration of both serotonin and NE in rat brain, and that the signs of acute toxicity resemble serotonin poisoning in the presence of an MAO inhibitor. Aziz and Knowles (1973) observed that these toxic signs resemble those produced by sympathomimetic agents including known MAO inhibitors.

Moderate toxicity to mammals has been reported. Acute oral LD_{50} values of 625 and 162 ppm (mg/kg of body weight) have been reported by Kenaga and Allison (1969) for the rabbit and rat, respectively. In view of this toxicity to mammals and of the possibility that sympathetic or serotonergic mechanisms were involved, it was of interest to determine whether or not interference with these mechanisms would affect the lethality of chlordimeform. This information would be of interest if the interference decreased toxicity, as the compounds which did so would be of possible antidotal value. If drugs of this nature increased the toxicity of chlordimeform, it would be of value to be aware of this inasmuch as many commonly used therapeutic agents affect NE and/or serotonin metabolism and their actions at their respective receptors.

II. Methods.

Two experiments were carried out to determine whether drugs which affect amine metabolism and actions influence the acute lethality of chlordimeform. In both experiments, the LD_{50}'s of chlordimeform in rats in the presence and absence of several drugs were determined.

In one experiment the effects of reserpine, methysergide and phentolamine on chlordimeform lethality in rats were determined. Reserpine in the dose and dosage schedule used depletes both norepinephrine and serotonin from their respective storage sites (Pletscher et al., 1956; Alpers and Shore, 1969; Dixit, 1971). The dose of phentolamine used selectively blocks alpha-adrenergic receptors (Lockett et al., 1969), while that of methysergide selectively blocks serotonergic receptors (Jespersen and Scheel-Krug, 1973). In this experiment 200 white male Holtzman rats were randomly divided into five equal groups. One group received reserpine (Serpasil for injection, Ciba) 48 hr (2.5 mg/kg) and 24 hr (1 mg/kg) prior to the administration of chlordimeform. Three other groups received either methysergide (3 mg/kg in normal saline), phentolamine (10 mg/kg in normal saline), or both drugs 25 min prior to the injection of chlordimeform. The control group received no drug prior to the injection of chlordimeform.

In the other experiment the effects of p-chlorophenylalanine, DL-α-methyl-p-tyrosine and phenylephrine on chlordimeform lethality were examined. The dose and dosage schedule of p-chlorophenylalanine used was reported by Yamori and coworkers (1972) to lower brain-stem serotonin to undetectable values while causing only a slight decrease in brain-stem NE. Boakes and coworkers (1972) reported that DL-α-methyl-p-tyrosine causes a selective depletion of NE from rat brain. Phenylephrine causes a direct stimulation of alpha-adrenergic receptors.

In this experiment, white male rats from Charles River Breeding Laboratories were divided into three treatment groups of 54 rats each and a control group of 48 rats. Rats in one treatment group were given 100 mg/kg p-chlorophenylalanine daily for 3 days prior to the administration of chlordimeform. Rats in the second group were given 500 mg/kg DL-α-methyl-p-tyrosine 20 hours prior to chlordimeform. Rats in the third group received 1 mg/kg phenylephrine immediately after chlordimeform. Rats in the control group received chlordimeform only. Six rats from each of the three treatment groups were given no chlordimeform, and were observed throughout the experiment.

All drugs in both experiments were injected intraperitoneally except reserpine, which was given intramuscularly. Chlordimeform was injected undiluted at appropriate dosage levels, and the resulting lethalities observed 1, 3, and 24 hours later. The LD_{50}'s were determined from curves plotted from mortality at each chlordimeform dosage level, using the maximum likelihood method of Finney (1971).

III. Results.

Rats that received only chlordimeform showed signs of central stimulation. Signs of central stimulation were more marked in those that had also received phenylephrine. No rats that received the pretreatment drugs alone died.

The length of time between injection of chlordimeform and death of the rats that died was dose related. Those receiving large doses ($\approx$ LD_{80}) survived only about 15 min, while those dying after small doses ($\approx$ LD_{20}) survived for approximately an hour. All animals that died during the 24-hour observation period did so within the first 3 hours for the reserpine-treated group, and within the first 2 hours for all other groups. Although the exact time from injection of the poison until death was not recorded for each individual animal, it was our impression that rats pretreated with the amine receptor blockers died more quickly than control rats.

None of the drugs used in an attempt to modify the lethality of chlordimeform significantly affected the LD_{50} (Tables 1 and 2).

TABLE 1. Effects of Pretreatment with Reserpine, Methysergide, or Phentolamine on the Lethality of Chlordimeform in Male Rats[a]

Pretreatment	Chlordimeform LD_{50}[b] (mg/kg)	95% Confidence Limits of the LD_{50}	Relative Lethality[c]	95% Confidence Limits of Relative Lethality
None	128	(103-149)	1	--------
Reserpine,[c]	138	(117-171)	0.89	0.71-1.12
Methysergide,[d]	107	(91-129)	1.15	0.92-1.44
Phentolamine,[e]	116	(99-142)	1.06	0.84-1.32
Phentolamine, and methysergide[f]	107	(89-152)	1.18	0.94-1.46

a. Holtzman, Madison, WI.
b. at 24 hours after chlordimeform by the method of Finney (1971).
c. im 2.5 mg/kg (48 hr) and 1 mg/kg (24 hr) prior to chlordimeform.
d. ip 3 mg/kg 25 min prior to chlordimeform.
e. ip 10 mg/kg 25 min prior to chlordimeform.
f. ip, phentolamine, 10 mg/kg; methysergide, 3 mg/kg, 25 min prior to chlordimeform.

From Robinson et al., 1975.

TABLE 2. Effects of p-chlorophenylalanine, DL-α-methyl-p-tyrosine or Phenylephrine on the Acute Lethality of Chlordimeform in Male Rats [a]

Drug Treatment	Chlordimeform LD_{50} [b] mg/kg	95% Confidence Limits of the LD_{50}
Control	238	202-271
p-chlorophenylalanine[c]	238	213-263
DL-α-methyl-p-tyrosine[d]	233	204-275
Phenylephrine[e]	241	220-271

a. Charles River Breeding Laboratories, Wilmington, MA.
b. at 24 hours after chlordimeform by the method of Finney (1971).
c. ip 100 mg/kg for 3 days prior to chlordimeform.
d. ip 500 mg/kg 20 hours prior to chlordimeform.
e. ip 1 mg/kg immediately after chlordimeform.

From Robinson and Smith, 1977.

...lethality of chlordimeform varied greatly in the two experiments, in which rats from two different sources were employed. Such a strain difference is not unusual. Rats from these two suppliers have been shown by Stavinoha and coworkers (1969) to react differently to chronic poisoning by the organophosphate insecticide Di-Syston (disulfoton).

IV. Discussion.

The metabolism and excretion of chlordimeform by rats is quite rapid. Within 12 hours after the oral administration of ^{14}C-labeled chlordimeform, over 70 percent of the administered radioactivity has appeared in the urine, and approximately 4 percent has appeared in the feces, according to Knowles and Sen Gupta (1970). Knowles and Roulston (1972) found that less than 17 percent of this labeled material in the urine is unmetabolized or only demethylated. These are the only forms capable of exerting appreciable activity. Thus chlordimeform should not be expected to exert toxicity over an extended period of time, unless it causes initial, irreversible effects. In our experiments it was found that the rats that died did so within a fairly short time, as would be expected with a toxicant which is rapidly inactivated and excreted.

The observations by other investigators that the toxic signs of acute poisoning resembled those of acute serotonergic or adrenergic stimulation were reinvestigated in these two experiments. The compounds used affect selectively the adrenergic or serotonergic neuroeffector systems. Those that modify adrenergic nerve function will be discussed first (Fig. 1).

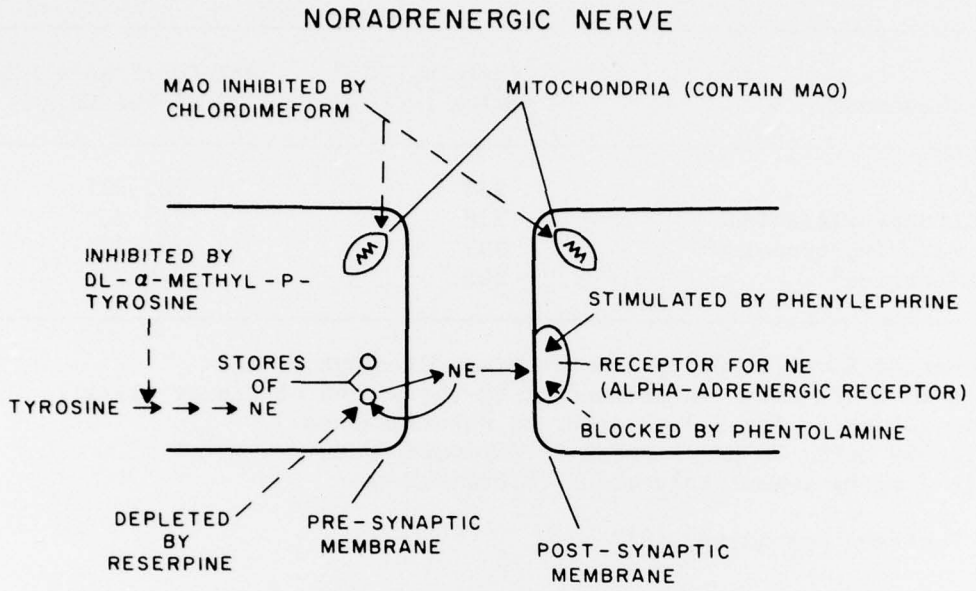


FIGURE 1.

After NE is released by nerve impulses from the pre-synaptic membrane, some of it combines transiently with its receptor to initiate post-junctional activity. An appreciable amount of NE is actively taken back into the adrenergic nerve, and part of this reenters the pre-synaptic granules to be used again.

Some NE diffuses into mitochondria where it may be inactivated by MAO, an enzyme which oxidatively deaminates it. Chlordimeform inhibits MAO, and thus allows the buildup of NE in the region in which it is released. The compound DL-α-methyl-p-tyrosine inhibits the synthesis of NE by inhibiting the enzyme, tyrosine hydroxylase. This decreases the quantity of NE available, without appreciably reducing serotonin levels. This should reduce lethality resulting from the acute buildup of NE. Phentolamine blocks the alpha-adrenergic receptor and thus should be able to reduce lethality resulting from acute stimulation of these receptors by the accumulated NE. Phentolamine also reduces reuptake of NE into adrenergic nerves and thus would contribute to NE accumulation, but the receptor blocking effect would predominate. Phenylephrine is a directly acting agonist at the alpha-adrenergic receptor. If stimulation of alpha-adrenergic receptors is a major contributor to the lethality of chlordimeform, phenylephrine should increase chlordimeform lethality. Because no drug affecting the adrenergic neuroeffector system affected the lethality of chlordimeform, it seems that the effects of MAO inhibition on adrenergic nerve function contributes little to chlordimeform lethality.

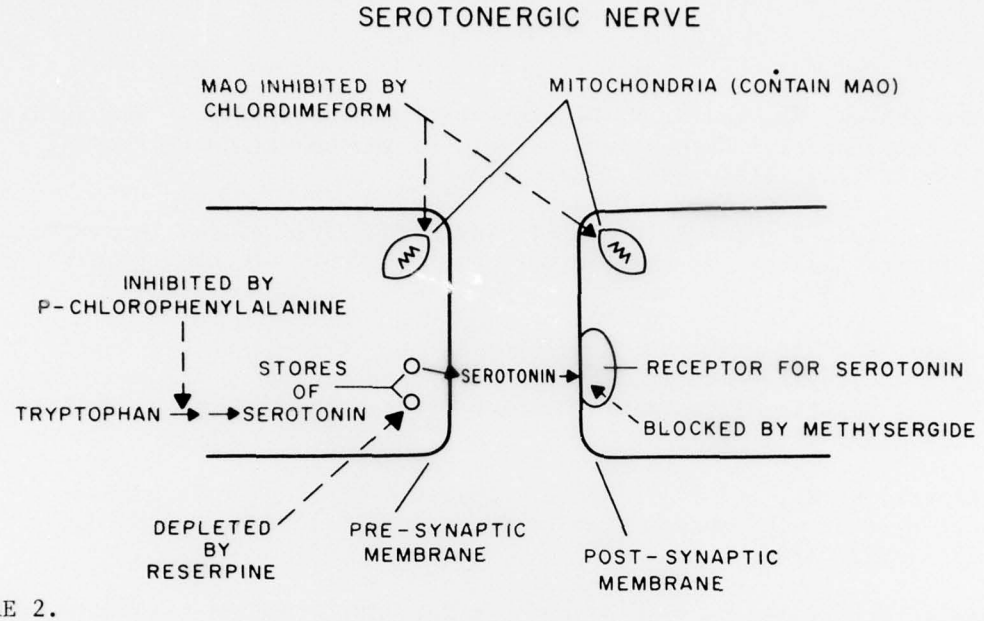


FIGURE 2.

In a similar manner, the effects of compounds that affect serotonergic nerve function were observed (Fig. 2). Inhibition of MAO by chlordimeform also causes accumulation of serotonin, as MAO also deaminates and thus inactivates serotonin. Depletion of serotonin to reduce the quantity available for accumulation was accomplished by using p-chlorophenylalanine, which selectively interferes with serotonin synthesis. Methysergide was used to specifically block the serotonin receptor. If serotonin accumulation played a major role in chlordimeform lethality, both serotonin depletion and serotonergic receptor blockade should have afforded some protection. Because this did not occur we infer that serotonin accumulation subsequent to MAO inhibition does not contribute much to chlordimeform lethality in the rat.

In like fashion, neither the depletion of both NE and serotonin by reserpine, nor the blockade of both serotonergic and adrenergic receptors with methysergide and phentolamine given at the same time, altered the LD_{50} of chlordimeform.

We conclude from these experiments that although MAO inhibition may contribute to the symptomatology of acute chlordimeform poisoning, it does not play a major role in the relatively sudden deaths that result from lethal doses.

Thus it would appear that none of the drugs tested shows promise in the treatment of acute chlordimeform poisoning. Likewise, it is unlikely that aerial applicators or others would incur extra risk if exposed to chlordimeform while taking any of those agents tested that are in current use for therapeutic purposes.

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