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MECHANISMS OF ACTION OF THE INSECTICIDE ENDRIN

FEDERAL AVIATION AGENCY
AVIATION MEDICAL SERVICE
AEROMEDICAL RESEARCH DIVISION
CIVIL AEROMEDICAL RESEARCH INSTITUTE
OKLAHOMA CITY, OKLAHOMA

AUGUST 1963
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THOMAS E. EMERSON, JR.
CHARLES M. BRAKE
LERNER B. HINSHAW

Environmental Physiology Branch
Civil Aeromedical Research Institute

63-16

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Thomas E. Emerson, Jr., Charles M. Brake, and Lerner B. Hinshaw

Acute lethal and sub-lethal poisoning by chlorinated hydrocarbon insecticides has been reported in man (1-12) and animals (11-17). Signs and symptoms following absorption of large amounts of chlorinated hydrocarbon insecticide, include hyperexcitability, tremors, ataxia, tonic-clonic convulsions, dyspnea, coma and not infrequently death (1, 5, 13). Fever (1, 5, 6, 8) and gastrointestinal disturbances (1, 12) have also been noted clinically. Headache, blurred vision, ataxia, tremors and mental confusion often accompany absorption of smaller amounts of these insecticides. Hematological alterations are not well defined. Clinical test on patients, ordinarily carried out several days after exposure, indicate variable effects on erythrocyte (1, 6, 8) and leukocyte (1, 2, 5-8) concentration.

Chlorinated hydrocarbon insecticides include endrin, dieldrin, aldrin, chlordane, lindane, and DDT, among others. They accumulate in body fat (12, 18-20) and fatty tissue of the liver, kidney and brain (21). Endrin, the most potent member of this group (22), has received little attention and was chosen for the present study. It is insoluble in water, but soluble to varying degrees in oil; absorption is by ingestion, inhalation or through the unbroken skin (13). Little is known concerning the cardiovascular changes following acute exposure to lethal amounts of endrin insecticide. The following experiments were therefore undertaken to determine the cardiovascular effects of endrin.

METHODS

In thirty experiments male and female mongrel dogs weighing from 10 to 19 kg were intravenously anesthetized with sodium pentobarbital (30 mg/kg body weight), and studied as described below.

Group 1 — General systemic effects of endrin

A. Initial experiments. Lethal amounts of endrin, 10 mg/kg body weight in 95% ethanol (25 mg/ml), were infused intravenously at 0.5 ml/minute in four experiments. Alcohol blank infusions at the rate and volume used with endrin were also administered.

A femoral vein was cannulated with polyethylene tubing for drug administration and for obtaining blood samples. Systemic arterial blood pressure and heart rate were continuously monitored through a cannulated femoral artery with a Statham pressure transducer and recorded on a Sanborn direct-writing recorder. Rectal temperature was measured using either a rectal probe and telethermometer or a mercury thermometer. Blood PH was measured with a Beckman Expanded scale pH meter. Hematocrits were determined in 1 cc Wintrobe tubes centrifuged at 3,000 rpm for 30 minutes. Leukocyte and differential counts with Wright’s stain were carried out using standard techniques.
It was necessary to give large amounts of sodium pentobarbital after endrin administration.

### B. Experiments with succinylcholine

The following experiments were carried out to avoid the depressant effects of additional barbiturate. Five dogs were given 3–10 mg of succinylcholine chloride (Anectine*) intravenously to prevent convulsions. Three animals received this drug several minutes before endrin, while it was given after endrin to two. Artificial respiration was necessary and the rate was usually adjusted in an effort to maintain blood pH within the physiological range. Except for a tracheotomy and artificial respiration, these animals were treated identically to those in group 1-A.

### C. Control experiments

Six animals were treated as in 1-B, except that endrin was not given.

### RESULTS

#### Group 1 — General Systemic effects of endrin

**A. Initial experiments.** Severe tonic-clonic convulsions usually commenced within five to ten minutes after the beginning of endrin infusion. Convulsions, as well as hyperexcitability to stimulation and copious, mucoid salivation, lasted until death. Convulsions could be initiated by a sharp sound. Because of technical difficulties ensuing from the violent convulsions and hyperexcitability following endrin administration, it was necessary to give repeated injections of sodium pentobarbital (25-50 mg per injection) every few minutes during the first 60 minute post-endrin period. Although each injection of barbiturate usually decreased arterial blood pressure the animals' tolerance to this drug was greatly enhanced after endrin.

Figure 1 and Table 1-A shows the measured parameters. Bradycardia, followed by a return towards or above control value, was seen in each experiment. Mean systemic arterial blood pressure always decreased initially, but increased toward the control level in two experiments. Increased rectal temperature, hemococoncentration, decreased venous blood pH and increased leukocyte concentration also occurred. Leukocytosis always resulted from increased neutrophil concentration. Immature neutrophils were evident with the neutrophilia. Hemolysis was present in every post-endrin hematocrit sample. Alcohol blank infusions had no cardiovascular effects and did not cause hemolysis.

Table 1-A depicts mean values for differential leukocyte counts. The trend was toward neutrophilia. The appearance of a number of immature neutrophils also was noted.

**B. Experiments with succinylcholine.** Succinylcholine completely prevented convulsions in each experiment. Data shown in Figure 2 and Table 1-B indicate that the results from these experiments were similar to those of the preceding studies with the exception of arterial blood pressure changes. In this series, arterial pressure always increased initially, but subse-
quently fell to hypotensive levels in all but one study. Blood pH also decreased more and hemoconcentration was more pronounced in these animals than in the previous group. Cardiovascular alterations exhibited here were presumably not related to succinylcholine muscle relaxant as demonstrated by control experiments and reports in the literature (23-25). In some of these animals bradycardia was replaced by tachycardia in a manner resembling vagal escape. Following this phenomenon the heart rate would often oscillate between bradycardia and tachycardia.

C. Control experiments. Figure 3 shows data from six control animals receiving no endrin. No changes comparable to those seen in the dogs which received endrin were demonstrated. Mean values for leukocyte differentials are presented in Table 1-C.

Group 2 — Effect of endrin on heart rate

Figure 4 shows mean values of control and post-endrin heart rates. Atropine, injected when the post-endrin bradycardia was pronounced, was followed within 30 seconds by an increased heart rate to near control levels. Figure 5 shows portions of photographed records from two studies demonstrating immediate reversal of bradycardia following intravenous injection of Atropine.

Group 3 — Effect of endrin on cerebrospinal fluid pressure

Figures 6 and 7 (graphed data and photographed record respectively) show the development of increased cerebrospinal fluid (CSF) pressure as well as arterial hypertension and bradycardia. Cerebrospinal fluid pressure elevation precedes arterial hypertension, but may follow the appearance of bradycardia. Figure 8 shows photographed portions of two records in which the elevated CSF pressure was lowered by fluid withdrawal to approximately zero mm Hg for several minutes and subsequently returned to the elevated level. No significant effect on arterial blood pressure or heart rate was demonstrated. In the lower record, intracranial fluid pressure is also shown. Lowering CSF pressure by fluid withdrawal at the cisterna magna level resulted in an equivalent decrease in intracranial fluid pressure measured in the subarachnoid space.

In three experiments in which sagittal venous sinus (SVS) pressure was monitored, it was seen to increase rapidly with CSF pressure elevation while peripheral internal jugular vein pressure did not change. It was not possible to determine which pressure rise occurred first. Transmitted pulse pressure in the SVS and CSF increased significantly following endrin, the greater increase being in the SVS tracing. Lowering CSF pressure had no appreciable effect on SVS pressure. Sagital venous sinus pressure could be lowered only a few mm Hg by withdrawing blood from the SVS; however, pressure changes in the sinus were followed closely by CSF pressure changes. Hypertension or bradycardia was never significantly affected by rapidly decreasing CSF pressure via fluid withdrawal, nor were these phenomena prevented by preventing CSF pressure from increasing. Maintaining CSF pressure at control level did not prevent the rise in SVS pressure.

DISCUSSION

Cardiovascular alterations produced by acute endrin poisoning in the dog include hypertension and severe bradycardia. The fact that bradycardia and hypotension may develop simultaneously (Group 1-A), or that bradycardia may precede hypertension (Group 1-B) indicates the independence of these two phenomena. The initial hypotension exhibited in some dogs was apparently caused by repeated injections of sodium pentobarbital used to control the convulsions and hyperexcitability.

Bradycardia, reversible with Atropine, was a consistent finding. It appeared to result from increased vagal activity and/or a potentiation of acetylcholine. Increased acetylcholine activity could be related to the fall in pHi since cholinesterase activity decreases with decreasing pH. This phenomenon has also been observed in animals acutely stressed with dieldrin (16) and aldrin (17). Bradycardia, copious mucoid salivation, hypertension, convulsions and other manifestations following endrin suggest that both sympathetic and parasympathetic nervous systems are hyperactive after endrin. Although elevated cerebrospinal fluid (CSF)
pressure can produce bradycardia and hyper-
tension (26, 27), this relationship was appar-
ently not observed in the present study. Acutely
lowering the elevated CSF pressure to control
level by fluid withdrawal or preventing CSF
pressure from increasing did not alter the de-
gree of bradycardia or hypertension. Cerebral
venous blood pressure alterations may have
been associated with the cardiovascular re-
sponses after endrin. Maintaining CSF pres-
sure at near control level did not prevent ele-
vation of sagittal venous sinus (SVS) pressure.
Increased cerebral venous blood pressure may
decrease the arteriovenous pressure difference
across the cerebral vasculature and produce
cerebral hypoxia if of sufficient magnitude.
Hypoxia of the medulla could contribute to
both bradycardia and hypertension. Increased
SVS pressure could result from cerebral arter-
iolar dilatation or cerebral venous constriction,
which would increase brain volume and CSF
pressure. Extracerebral arterial blood pressure
increase followed the rise in SVS pressure and
central venous blood pressure did not increase
after endrin. Therefore, these factors do not
appear to contribute to the initial SVS pressure
elevation.

Endrin appears to have a direct action on
the medulla, as bradycardia often develops be-
fore CSF or SVS pressure increase. Convulsions
and hyperexcitability were probably caused by
endrin acting directly on the motor cortex
and/or spinal cord. Increased body temper-
ature, which was moderate except in two cases,
could have resulted from a central action of
endrin and altered metabolic rate. Convulsions
also appear to contribute since the rise in
temperature seems greater in convulsion ani-
mals which were not treated with succinyl-
choline.

The majority of animals exhibited large in-
creases in the concentration of leukocytes.
Conditions of manual work or exercise are
accompanied by leukocytosis (28, 29) which
is consistent with the findings in the convulsive
dogs. However, convulsions are apparently not
prominently involved because the animals
which did not exhibit convulsions (succinyl-
choline treated) showed a greater leukocytosis
than the convulsing dogs. Both mobilization
of stored leukocytes and increased bone marrow
production, indicated by the appearance of im-
mature neutrophils in the plasma, appear to
have contributed to the increased plasma
leukocyte concentration.

The hemoconcentration observed in most ani-
mal could result from (a) release of erythro-
cytes from the spleen (30, 31), (b) increased
capillary permeability, or (d) stimulatory ac-
tion of endrin on erythropoetic bone marrow
tissue.

The trend toward acidosis during endrin in-
toxicatation did not appear to be of respirator-
origin since increasing ventilatory rate did not
prevent the decreased pH. Decreased perfusion
and/or increased metabolic rate could explain
the acidosis.

A schema of the possible mechanisms of
action of endrin insecticide is presented in
Figure 9.

SUMMARY

Cardiovascular effects of endrin insecticide
are obscure. Experiments to investigate these
phenomena were carried out on dogs and sug-
gested mechanisms of action have been pro-
posed. Results show that acute administration
of endrin produces bradycardia, hypertension,
copious salivation, hyperexcitability, tonic-
clonic convulsions, increased body temperature,
leukocytosis, hemoconcentration and decreased
blood pH. Cerebral venous pressure and cere-
brospinal fluid pressure elevations are also
prominent features of endrin poisoning. Al-
though most of these effects appear to be
caused by endrin acting directly on the central
nervous system some may result secondarily
from altered cerebral hemodynamics. A schema
of the possible mechanism of action of endrin
has been presented.
REFERENCES

5. A. A. Buck, and L. Pfannemuller, Arch Toxicol. 16, 328 (1957).
Figure 1. – Cardiovascular and hematological alterations produced by endrin insecticide are shown on the ordinate. Time, before and after endrin infusion, is indicated on the abscissa. Endrin infusion was started at the arrow.
Figure 2.—Cardiovascular and hematological alterations produced by endrin in Anectine treated dogs are plotted on the ordinate. Time, before and following endrin infusion, is indicated on the abscissa.
Figure 3. — Cardiovascular and hematological measurements obtained from animals receiving no endrin are plotted on the ordinate against time on the abscissa.
Figure 4.—Mean values (± S. E.) of heart rates before and after endrin and atropine respectively are shown. Bradycardia produced by endrin is immediately reversed by atropine.
Figure 5. — Records from two typical experiments are presented demonstrating reversibility of the post-endrin bradycardia by atropine.
Figure 6.—Development of bradycardia, elevated cerebrospinal fluid pressure, and hypertension following endrin administration is shown in six animals.
Figure 7. Records from two experiments showing the development of cardiopulmonary failure and the effect of endrin. 

Heart Rate (beats/min.)

Arterial Blood Pressure (mm Hg)

Cerebrospinal Fluid Pressure (mm Hg)

Time (min.)

Pre-Endrin

Post Endrin
Figure 8.—Records from two typical experiments demonstrating no effect on bradycardia or hypertension by lowering the elevated cerebrospinal fluid pressure. Lower record also shows that intracranial fluid pressure (measured in the subarachnoid space) changes follow spinal fluid pressure changes closely.
Figure 9. — A possible schema of action of endrin based on results from present *-...
TABLE 1

TABLE 1-A

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TABLE 1: A-Mean leukocyte differential counts (±S.E.) from dogs receiving endrin; B-Mean leukocyte differentials (±S.E.) for dogs receiving endrin and anectine; C-Mean leukocyte differentials (±S.E.) from control animals receiving no endrin.
Cardiovascular effects of endrin insecticide are obscure. Experiments to investigate these phenomena were carried out on dogs and suggested mechanisms of action have been proposed. Results show that acute administration of endrin produces bradycardia, hypertension, copious salivation, hypereexcitability, tonic-clonic convulsions, increased body temperature, leukocytosis, hemococoncentration and decreased blood pH. Cerebral venous pressure and cerebrospinal fluid pressure elevations are also prominent features of endrin poisoning. Although most of these effects appear to be caused by endrin acting directly on the central nervous system some may result secondarily from altered cerebral hemodynamics.

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