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EFFECT OF AN ANTIHISTAMINE ON EARLY TRANSIENT INCAPACITATION
OF MONKEYS SUBJECTED TO 4000 RADS OF MIXED
GAMMA-NEUTRON RADIATION

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FOREWORD
(Nontechnical summary)

Minutes after receiving 4000 rads of pulsed mixed gamma-neutron radiation, monkeys consistently experience a period in which they are physically or mentally unable to perform a learned task. This period generally lasts 5 to 30 minutes and is frequently characterized by complete unresponsiveness or unconsciousness, followed by partial or complete recovery and eventually permanent incapacitation and death.

This early transient incapacitation (ETI) correlates well with a severe drop in blood pressure believed to be caused in large part by histamine. Hypotension of this magnitude can result in a decrease in cerebral blood flow sufficient to impair brain metabolism such that unconsciousness occurs.

This experiment was designed to determine whether blocking the histamine receptor sites with antihistamine will reduce or prevent the severe hypotension and concomitant ETI experienced by monkeys at this dose of radiation.

Although untrained monkeys were used, their behavior and responses to auditory stimuli were recorded and collated with continuously recorded blood pressure measurements.

The eight monkeys of the control group were given only normal saline. Ten monkeys were given 10 mg of antihistamine, and an additional seven monkeys were given 20 mg of antihistamine. Each animal then received 4000 rads of mixed gamma-neutron radiation in a single pulse.

All of the saline-treated, control animals had severe hypotension; mean arterial pressure fell to about 50 percent of normal. Further, all of the control animals, except one, suffered ETI (unconsciousness or complete unresponsiveness).

Hypotension of the drug-treated animals was less severe than that of the control group and was of shorter duration. Only 1 of the 17 drug-treated animals suffered ETI. The results show that ETI of monkeys receiving 4000 rads can be eliminated by the infusion of chlorpheniramine to prevent a severe drop in blood pressure.

The average survival time of the drug-treated animals was significantly longer than that of the controls.

ABSTRACT

An antihistamine, chlorpheniramine maleate, was used in monkeys to ameliorate the severe hypotension and to prevent signs of the early transient incapacitation (ETI) frequently associated with supralethal doses of ionizing radiation. Twenty-five monkeys (Macaca mulatta) were given 4000 rads of mixed gamma-neutron radiation delivered as a single pulse of approximately 50 milliseconds duration. Eight of the animals served as controls and received only normal saline injections; 10 animals were each injected with 10 mg of the antihistamine 30 minutes before irradiation; and a third group of seven animals each received 10 mg of antihistamine 60 minutes before irradiation plus 10 mg of antihistamine 30 minutes before irradiation. Blood pressure was monitored from time of injection until death, and clinical symptoms were recorded until 1 hour after irradiation. All but one of the antihistamine-treated animals remained alert and responsive to auditory stimuli with no evidence of ETI. The control animals became unconscious and unresponsive and suffered a longer and more severe hypotension than the antihistamine-treated animals. The average survival time of the antihistamine-treated animals was significantly greater than that of the control animals.

I. INTRODUCTION

Many effects of radiation seen in monkeys following 2500- to 30,000-rad doses may be attributable to histamine. Hypotension, erythema, gastrointestinal manifestations, etc. can be produced by histamine. Ellinger⁴ summarized these effects and cited evidence for the liberation of histamine in cells, the formation of new histamine, and the increase of histamine or histamine-like substances in skin and blood following irradiation.

The most marked, direct, cardiovascular effect of histamine on man and monkey is peripheral vasodilation. This dilation can cause hypotension so severe as to result in unconsciousness. Chapman and Young² have shown that the initial drop in blood pressure of irradiated monkeys (2500 rads) was associated with a decrease in cerebral blood flow to 30 percent of preirradiation values. Proportionate decreases in blood pressure⁶ and blood flow⁵ in man produce cerebral ischemia and unconsciousness. Chapman and Young² also noted that the cerebral blood flow depression corresponds closely in time with a period of early transient incapacitation (ETI); however, their work was done on partially anesthetized animals at a lower dose rate and total dose of irradiation than the work reported here.

After receiving 2500 to 30,000 rads, monkeys generally experience a sudden performance decrement beginning within 6 minutes and lasting up to 30 minutes. A temporary, partial or complete recovery often occurs; performance decrement from which there is no recovery then ensues shortly before death.

These experiments were designed to determine whether blocking the histamine receptor sites with antihistamine will reduce the severe hypotension and ameliorate

the performance decrement usually experienced by monkeys after 4000 rads of pulsed mixed gamma-neutron radiation.

II. METHODS AND MATERIALS

The monkeys used were 2- to 3-year-old Macaca mulatta, males and females, weighing 3 to 5 kg. They had all passed a 30-day quarantine period during which they were tested for tuberculosis and treated for any internal parasites. They were fed Purina monkey chow supplemented with fruit, and water was available at all times.

Three days before irradiation each monkey was anesthetized with sodium pentobarbital and catheters were inserted into a femoral artery and vein. The tip of the arterial catheter was advanced into the descending aorta and the venous catheter tip was inserted into the inferior vena cava to a level above the diaphragm. After surgery the animals were placed in restraining chairs where they remained until death.

Twenty-five animals were used. Ten of the animals were given 10 mg of antihistamine (chlorpheniramine maleate*) in 5 ml of normal saline 30 minutes before irradiation; seven animals were given 10 mg of antihistamine 60 minutes before irradiation and another 10 mg of antihistamine 30 minutes before irradiation. The eight control monkeys received only 5 ml of normal saline 30 minutes before irradiation. The intravenous route of administration was used in each instance.

Each monkey received 4000 ± 400 rads of mixed gamma-neutron radiation from the AFRRI-TRIGA reactor in a single pulse (pulse width at half maximum was 25 milliseconds). This dose was used as it is generally the lowest that consistently produces ETI in monkeys.

* Chlor-Trimeton, Schering Corporation, Bloomfield, New Jersey

Blood pressure was monitored from time of injection until death and clinical symptoms were recorded until 1 hour after irradiation.

Closed circuit television was used to observe, and video tape to record, the monkeys' actions and responses to auditory stimuli while in the exposure room. Mean arterial pressure was calculated as (systolic pressure + 2 diastolic pressure)/3.

III. RESULTS

Immediately following irradiation there was a sharp rise in blood pressure (25 to 50 mm Hg lasting 10 to 15 seconds) of the antihistamine and control animals (Figure 1). In some individual animals a second and third rise occurred at approximately 12-second intervals (Figure 1). The mean arterial pressure (MAP) of the antihistamine-treated and the control animals began to fall within 1 minute and at 2 minutes reached minimum values for the antihistamine-treated animals (Figure 2). The MAP of the control animals continued to drop, reaching a minimum at 5 minutes.

The MAP of the control animals never recovered to the preirradiation value, however, the MAP of the antihistamine-treated monkeys recovered to greater than preirradiation levels.

Six to eight minutes following irradiation all but one of the control monkeys became unresponsive to noise from the audio receiver in the exposure room and appeared unconscious for 5 to 30 minutes. Only one of the antihistamine-treated monkeys appeared unconscious; all the rest remained alert and all vomited except the one that appeared unconscious. The single control animal that had no signs of ETI was the only control animal that vomited. Pulse pressure of control animals

frequently decreased to less than 10 mm Hg for a short period of time very soon after irradiation (Figure 1C).

Survival times varied greatly within each of the groups (Table I), however, the survival times of the antihistamine-treated monkeys were significantly longer than those of the control group.

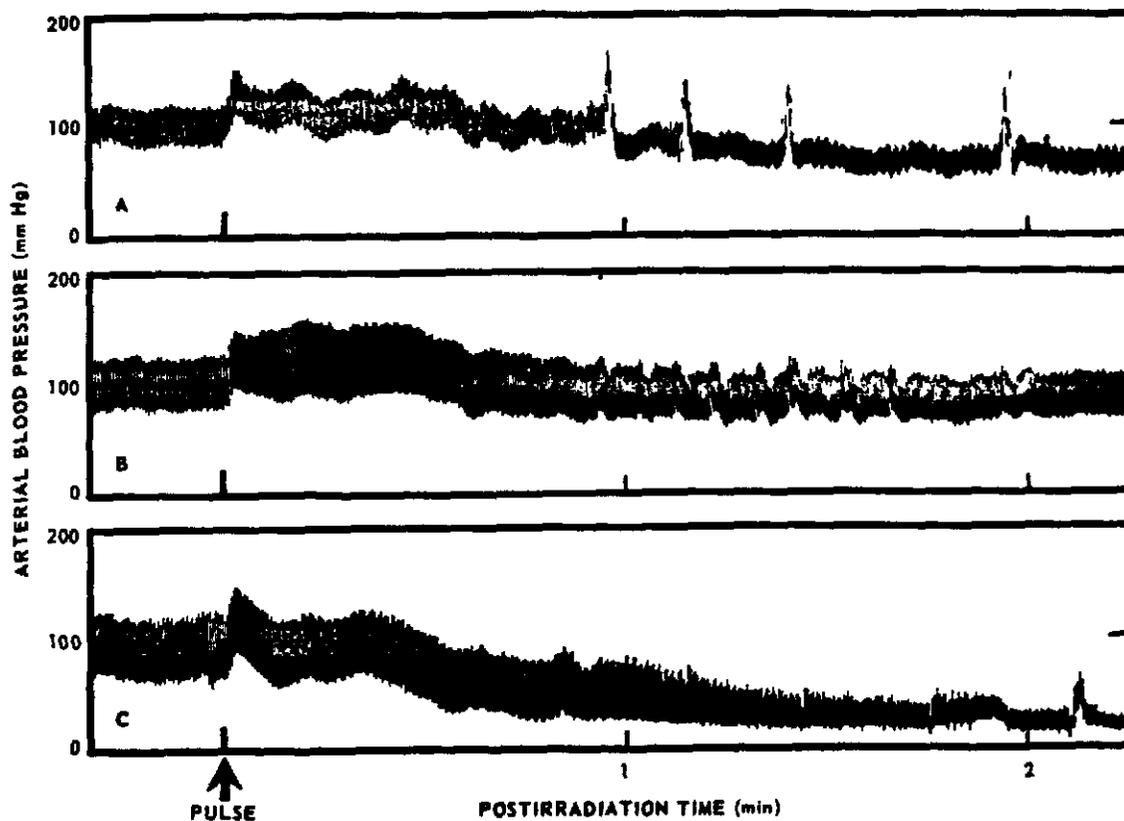


Figure 1. Characteristic blood pressure changes in monkeys treated with an antihistamine then given 4000 rads of mixed gamma-neutron radiation: (A) Monkey treated with 10 mg of chlorpheniramine 30 minutes before irradiation; (B) Monkey treated with 10 mg of chlorpheniramine 60 minutes before irradiation and an additional 10 mg 30 minutes before irradiation; (C) Control monkey

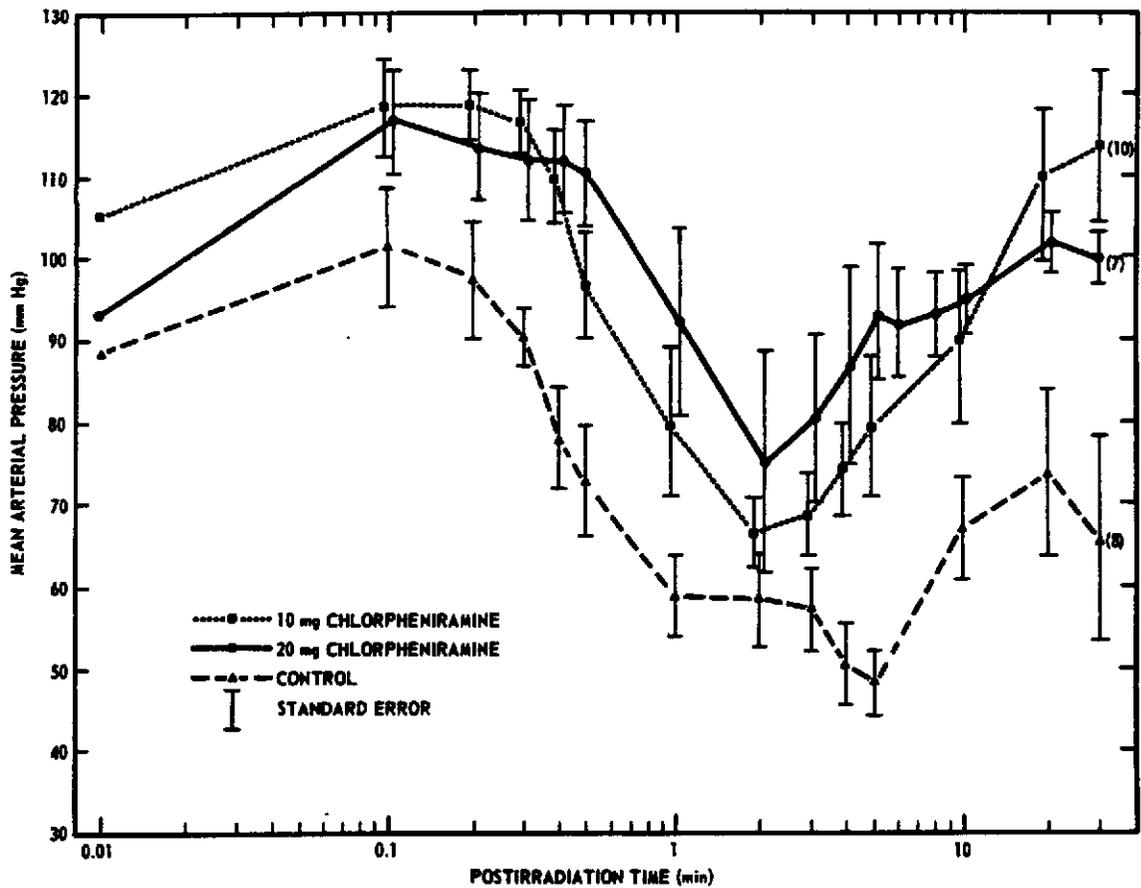


Figure 2. Postirradiation blood pressure changes in monkeys treated with an antihistamine then given 4000 rads of mixed gamma-neutron radiation

	Survival time hours (mean \pm S. E.)
Controls	2.9 \pm 1.2
Chlorpheniramine 10 mg	13.1 \pm 2.6
Chlorpheniramine 20 mg	23.2 \pm 4.7

Table I. Average Survival Times of Monkeys Treated with an Antihistamine then Given 4000 Rads of Mixed Gamma-Neutron Radiation

Probability that means are from same population:
 Controls vs chlorpheniramine (10 mg group) < 0.01
 Controls vs chlorpheniramine (20 mg group) < 0.01
 10 mg vs 20 mg chlorpheniramine group < 0.10

IV. DISCUSSION

Chlorpheniramine prevented signs of the ETI which usually occurs in monkeys following a 4000-rad dose of pulsed mixed gamma-neutron radiation. Hypotension that occurred in the antihistamine-treated animals was less severe and of shorter duration than that of the control animals. Normal blood pressure levels were re-established in 10 to 15 minutes in contrast to the blood pressure of the controls which never recovered to preirradiation levels.

Ellinger has summarized data showing that histamine is the causal agent of radiation-induced hypotension⁴ and cites evidence for the formation or liberation of histamine by irradiation.

Adrenergic amines have been reported to release histamine⁷ and Beck¹ has shown that in the isolated hind limbs of dogs, epinephrine and norepinephrine evoke an active and passive reflex dilatation, probably histamine induced, which is blocked centrally and peripherally by antihistamines.

The arterial blood pressure rise of 25 to 50 mm Hg immediately following irradiation (Figure 1) is probably due to the local effect of norepinephrine released from sympathetic postganglionic fibers. An alpha adrenergic blocking agent (Dibenzylamine) prevented this rise.* Further, the rise did not occur when norepinephrine stores had been depleted by reserpine administration.*

The release of histamine after irradiation could be due to the direct action of the radiation⁴ or indirectly through the action of amines¹ although hypotension still occurs after depleting norepinephrine stores.*

* Unpublished: Turns, J. E. and Doyle, T. F., Armed Forces Radiobiology Research Institute, Bethesda, Maryland 20014

Chapman and Young² have shown a close correlation between the suddenly decreased cerebral blood flow and onset of ETI in irradiated monkeys; however, work presently under way at this Institute with 2500 rads given as a single pulse has not shown such a close correlation. Cerebral blood flow in man is relatively independent of blood pressure until the pressure falls to about 50-60 percent of normal values, then the flow is inadequate to maintain cerebral oxygen requirements and ischemia and unconsciousness develop.^{5,6}

The blood pressure of the control animals fell to about 55 percent of normal values 5 minutes after irradiation. This minimum occurred approximately 1 minute before the previously reported average onset time of severe performance decrement.³

The accepted explanation of antihistaminic action is the competitive inhibition of histamine receptor sites. Antihistamines do not, however, repress the gastric secretory response to histamine. There is evidence of a histamine trapping or binding mechanism in the mucosa where the HCl secreting parietal cells are situated. The stimulatory effect of histamine on parietal cells to produce hydrochloric acid has been known for many years. If the liberated, circulating, histamine is blocked from peripheral receptor sites by antihistamines, more may be available for concentration by the mucosa with increased HCl production. This could explain why 16 of the 17 treated animals vomited and only one of the control animals vomited.

We have noted that irradiated monkeys that vomit have a better prognosis in respect to behavior and survival time than those that do not vomit. The only control animal that vomited had no signs of ETI and lived the longest of all control animals (19.5 h).

V. CONCLUSIONS

Pretreatment with chlorpheniramine maleate is of value in preventing the severe hypotension and concomitant ETI usually experienced by monkeys subjected to supralethal doses of ionizing radiation.

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13. ABSTRACT <p>An antihistamine, chlorpheniramine maleate, was used in monkeys to ameliorate the severe hypotension and to prevent signs of the early transient incapacitation (ETI) frequently associated with supralethal doses of ionizing radiation. Twenty-five monkeys (<u>Macaca mulatta</u>) were given 4000 rads of mixed gamma-neutron radiation delivered as a single pulse of approximately 50 milliseconds duration. Eight of the animals served as controls and received only normal saline injections; 10 animals were each injected with 10 mg of the antihistamine 30 minutes before irradiation; and a third group of seven animals each received 10 mg of antihistamine 60 minutes before irradiation plus 10 mg of antihistamine 30 minutes before irradiation. Blood pressure was monitored from time of injection until death, and clinical symptoms were recorded until 1 hour after irradiation. All but one of the antihistamine-treated animals remained alert and responsive to auditory stimuli with no evidence of ETI. The control animals became unconscious and unresponsive and suffered a longer and more severe hypotension than the antihistamine-treated animals. The average survival time of the antihistamine-treated animals was significantly greater than that of the control animals.</p>			

14 KEY WORDS	LINK A		LINK B		LINK C	
	ROLE	WT	ROLE	WT	ROLE	WT