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CHLORPHENIRAMINE AS A PROPHYLAXIS TO RADIATION-INDUCED PERFORMANCE DECREMENT IN THE MONKEY

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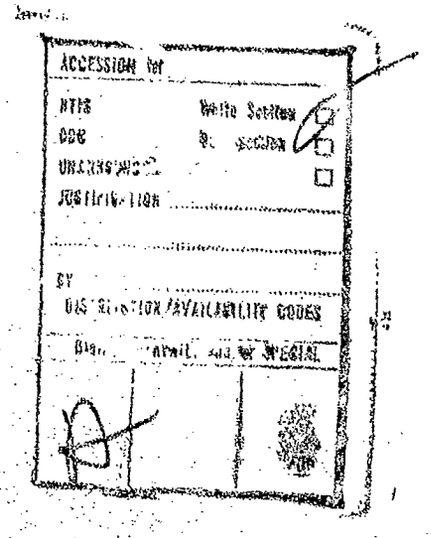

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13. ABSTRACT

The effectiveness of the antihistamine chlorpheniramine maleate in preventing the early performance decrement in monkeys following a supralethal dose of ionizing radiation was investigated. Twenty-five male monkeys (Macaca mulatta) were trained to perform a discrete trial, cued avoidance task. Ten of these monkeys were injected intravenously with isotonic saline 30 minutes before irradiation. Five monkeys were injected with 20 mg of chlorpheniramine and were performance tested 24 hours prior to irradiation. These five animals and 10 additional animals were then injected with 10 mg of chlorpheniramine at 60 minutes and at 30 minutes before irradiation. The monkeys were tested and their performance was recorded for 2 hours following a 4000-rad dose of mixed gamma-neutron radiation; blood pressure was monitored in 20 of the monkeys. The performance of the chlorpheniramine-treated monkeys was markedly superior to that of the saline-treated group during the first 30 minutes post-irradiation (the period generally associated with early transient incapacitation). With the exception of one group of five monkeys, the antihistamine-treated animals performed significantly better than the saline-treated monkeys during the entire 2-hour postirradiation observation period. The average blood pressure of the chlorpheniramine-treated monkeys was higher than that of the saline-treated monkeys throughout the observation period. These findings show that chlorpheniramine prevents the performance decrement and reduces the severity of hypotension observed in monkeys following a supralethal dose of ionizing radiation.

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FOREWORD
(Nontechnical summary)

An earlier study showed that the severe decline in blood pressure occurring in monkeys immediately following a supralethal dose (4000 rads) of ionizing radiation can be reduced or prevented by the preirradiation injection of a massive dose of an antihistamine, chlorpheniramine. The present study was designed to test the effectiveness of chlorpheniramine in preventing the performance decrement generally observed in monkeys following such a dose of radiation.

Twenty-five rhesus monkeys were trained to perform a simple cued avoidance task. Ten of the monkeys were injected with saline and the remainder with chlorpheniramine prior to a 4000-rad dose of mixed gamma-neutron radiation. Five monkeys were given 20 mg of chlorpheniramine and were performance tested 24 hours before irradiation and then this group and 10 other monkeys were given 10 mg of chlorpheniramine at 60 minutes and again at 30 minutes before irradiation. The performance of all monkeys was recorded for 2 hours postirradiation. Blood pressure was monitored during the same period in the saline-treated controls and in 10 of the antihistamine-treated animals. Early performance decrement consistently occurred in all the saline-treated monkeys following irradiation but was rare in the antihistamine-treated monkeys. The postirradiation blood pressure drop in the antihistamine-treated monkeys was not as great as that of the saline-treated group. Therefore, chlorpheniramine is effective both in preventing early performance decrement and in reducing the decline in blood pressure in monkeys immediately following a supralethal dose of ionizing radiation.

ABSTRACT

The effectiveness of the antihistamine chlorpheniramine maleate in preventing the early performance decrement in monkeys following a supralethal dose of ionizing radiation was investigated. Twenty-five male monkeys (Macaca mulatta) were trained to perform a discrete trial, cued avoidance task. Ten of these monkeys were injected intravenously with isotonic saline 30 minutes before irradiation. Five monkeys were injected with 20 mg of chlorpheniramine and were performance tested 24 hours prior to irradiation. These five animals and 10 additional animals were then injected with 10 mg of chlorpheniramine at 60 minutes and at 30 minutes before irradiation. The monkeys were tested and their performance was recorded for 2 hours following a 4000-rad dose of mixed gamma-neutron radiation; blood pressure was monitored in 20 of the monkeys. The performance of the chlorpheniramine-treated monkeys was markedly superior to that of the saline-treated group during the first 30 minutes post-irradiation (the period generally associated with early transient incapacitation). With the exception of one group of five monkeys, the antihistamine-treated animals performed significantly better than the saline-treated monkeys during the entire 2-hour postirradiation observation period. The average blood pressure of the chlorpheniramine-treated monkeys was higher than that of the saline-treated monkeys throughout the observation period. These findings show that chlorpheniramine prevents the performance decrement and reduces the severity of hypotension observed in monkeys following a supralethal dose of ionizing radiation.

I. INTRODUCTION

Immediately following large, supralethal doses of ionizing radiation, monkeys usually show a performance decrement, the severity of which is dose related.[8] Generally, the performance decrement of monkeys exposed to a 4-krad dose of mixed gamma-neutron radiation starts as early as 2 minutes after irradiation and lasts for 10 to 30 minutes with subsequent recovery to, or near, preirradiation levels of performance. This early transient incapacitation (ETI) is accompanied by severe systemic hypotension during which arterial blood pressure often decreases to less than 50 percent of normal.[4]

Ionizing radiation is known to release histamine, a powerful vasodilator which is capable of producing many of the more overt effects seen during ETI. An earlier study[4] showed that pretreating monkeys with a massive dose of an antihistamine, which acts by occupying receptor sites on target cells,[1,3] prevented the gross signs of incapacitation and significantly reduced hypotension during the ETI period; but the mechanisms by which this drug decreases ETI effects are not known.

The present study examines the effectiveness of chlorpheniramine in preventing the performance decrement of task trained monkeys following a single 4-krad dose of mixed gamma-neutron radiation.

II. MATERIALS AND METHODS

The animals used were 2- to 3-year old male monkeys (Macaca mulatta) weighing 3 to 5 kg. The care and maintenance of these monkeys have been described elsewhere.[4,8]

Each monkey was trained to perform a discrete trial, cued avoidance task. At the beginning of each trial, a 1-second warning tone and a 5.5-second cue light were presented simultaneously. The cue light appeared over one of two levers and indicated the correct response lever for that trial. If the animal failed to move the correct lever within the first 5 seconds of the trial, a 0.5-second electrical shock was administered to the monkey's tail. The shock and light terminated simultaneously, and a 4.5-second time-out followed. A correct response during the shock period permitted the animal to escape the remainder of the shock. Time between the onset of successive trials was 10 seconds. If the animal moved the correct lever within the first 5 seconds of the trial, the cue light was immediately extinguished and time-out was initiated, thereby permitting the animal to avoid the shock. Trials were presented on either of the two levers, in random order, an equal number of times within blocks of 100 trials (except that no lever was cued consecutively more than three times).

To minimize distraction, the animals were trained, irradiated, and tested in isolation cubicles. Each animal was trained until it could respond correctly, at least 90 percent of the time, to 2000 consecutive trials.

Twenty-five trained monkeys were divided into four experimental groups, as indicated below. The monkeys in groups A, B, and C had catheters inserted into their femoral arteries and veins 3 days before irradiation. The tips of the catheters were advanced a measured distance to the level of the diaphragm (the position was verified at necropsy). These catheters were used for recording blood pressure and administering drugs. Clotting of the catheters was prevented by refilling them with a 1 percent heparin solution twice daily, but no attempt was made to heparinize the animals.

The monkeys were medicated, as follows:

Group A. Ten monkeys received 10 ml of isotonic saline 30 minutes before irradiation, and served as the control group.

Group B. Five monkeys received 10 mg of chlorpheniramine (2 mg/ml of isotonic saline) 60 minutes before irradiation and another 10 mg of chlorpheniramine 30 minutes before irradiation.

Group C. Five monkeys were given 20 mg of chlorpheniramine (~5.7 mg/kg) 24 hours before irradiation. Their response to the cued avoidance task was then tested for 2 hours. These monkeys then received 10 mg of chlorpheniramine 60 minutes before irradiation and another 10 mg of chlorpheniramine 30 minutes before irradiation. (Each of the monkeys received a total of 40 mg (~11.5 mg/kg) of chlorpheniramine in the 24-hour preirradiation period.)

Group D. Five monkeys were used to evaluate the effect on the monkeys' performances of the general anesthesia (sodium Pentothal, 35 mg/kg, intravenously) and surgery used in the catheterization procedure. Catheters were not placed in the animals of this group. These monkeys were injected with 20 mg (~5.7 mg/kg) of chlorpheniramine in a superficial leg vein 60 minutes before irradiation.

All monkeys were given a 100-trial performance test beginning 25 minutes prior to receiving a midline tissue dose of 4000 ± 400 rads of mixed gamma-neutron radiation from the AFRRI-TRIGA reactor. The radiation was delivered as a single pulse of short duration (~50 msec).

Postirradiation performance testing began 5 seconds after the pulse. Each test period (block) consisted of 100 trials. The performance testing of all monkeys was

continued for 2 hours after irradiation unless death intervened. During this time they were visually monitored via closed-circuit television. Blood pressure was recorded for the monkeys in Groups A, B, and C. The average correct response for each 2-minute interval (10 trials) was calculated and plotted at the midpoint of that interval. After each block of 100 trials, there was a 3.4-minute rest period. Following the initial 2-hour postirradiation testing period, the monkeys of Group D were given a 100-trial test each hour until they died.

The results of this study were evaluated using the following criteria:

Performance decrement. The monkeys were trained to perform at or better than 90 percent correct response. Performance less than 90 percent correct was considered a performance decrement.

Early transient incapacitation (ETI). Failure to respond for four or more consecutive trials during the first 30 minutes postirradiation, followed by a resumption of task performance, was considered ETI.

Permanent complete incapacitation (PCI). A period in which the animal failed to respond was considered PCI, and terminated in death.

III. RESULTS

The postirradiation performance and mean arterial blood pressure of individual monkeys treated with isotonic saline or chlorpheniramine are shown in Figures 1 through 4. The average postirradiation performance of each treatment group is plotted in Figure 5 and the average blood pressure for each group is presented in Figure 6.

Performance and latency of response during the 2-hour period following chlorpheniramine administration (24 hours preirradiation) were not significantly different from the pretreatment values of the nonirradiated monkeys (Group C).

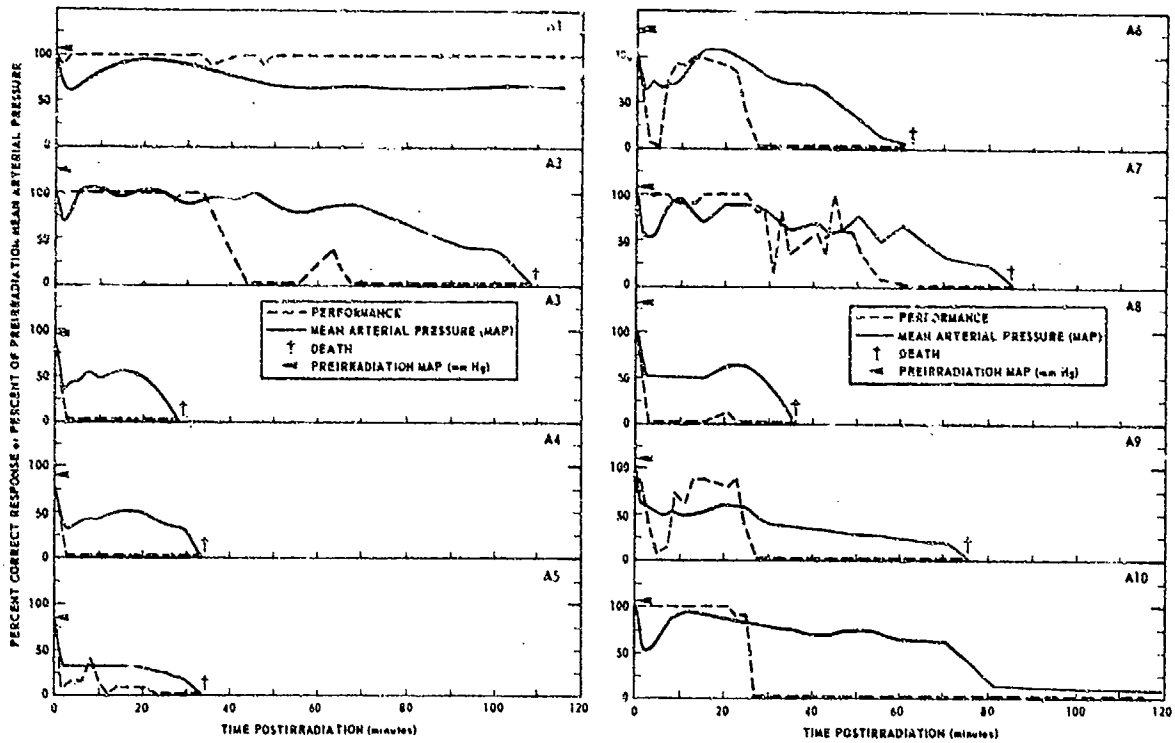

Figure 1. Performance and mean arterial blood pressure of saline-treated monkeys following a 4000-rad dose of mixed gamma-neutron radiation

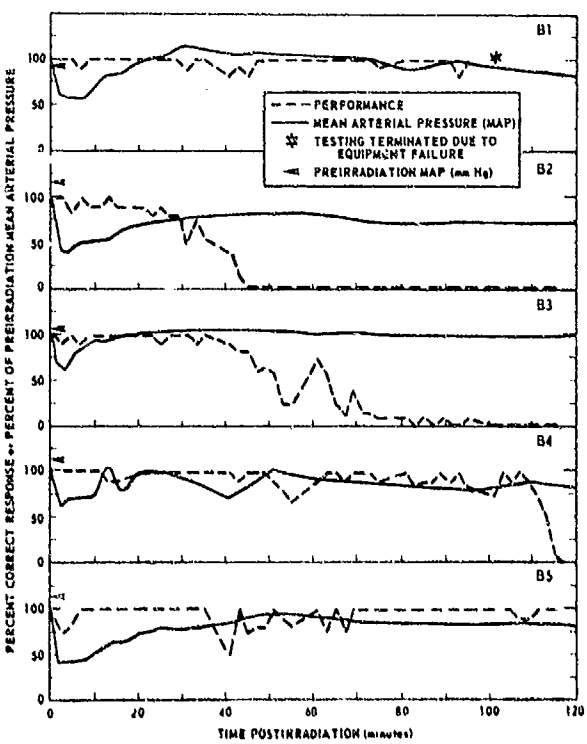

Figure 2.

Performance and mean arterial blood pressure of antihistamine-treated monkeys (10 mg chlorpheniramine 60 minutes and 10 mg chlorpheniramine 30 minutes preirradiation) following a 4000-rad dose of mixed gamma-neutron radiation

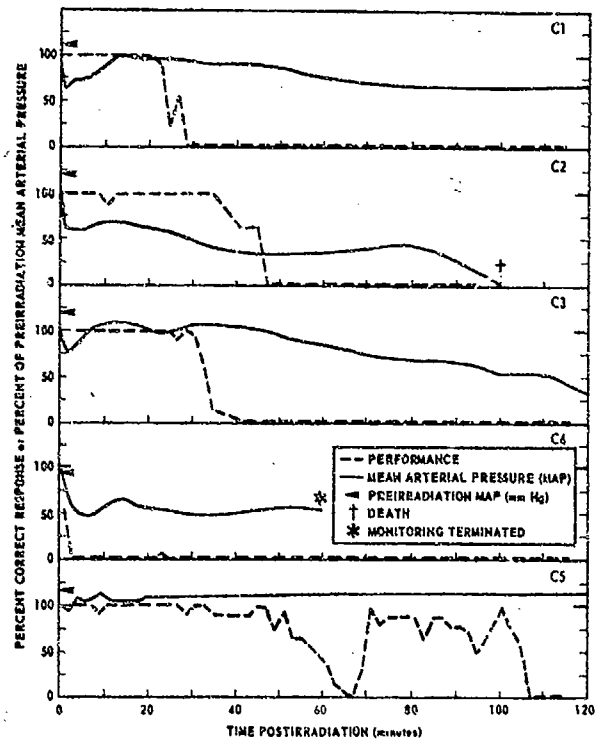

Figure 3.

Performance and mean arterial blood pressure of antihistamine-treated monkeys (20 mg chlorpheniramine 24 hours, 10 mg chlorpheniramine 60 minutes and 10 mg chlorpheniramine 30 minutes preirradiation) following a 4000-rad dose of mixed gamma-neutron radiation

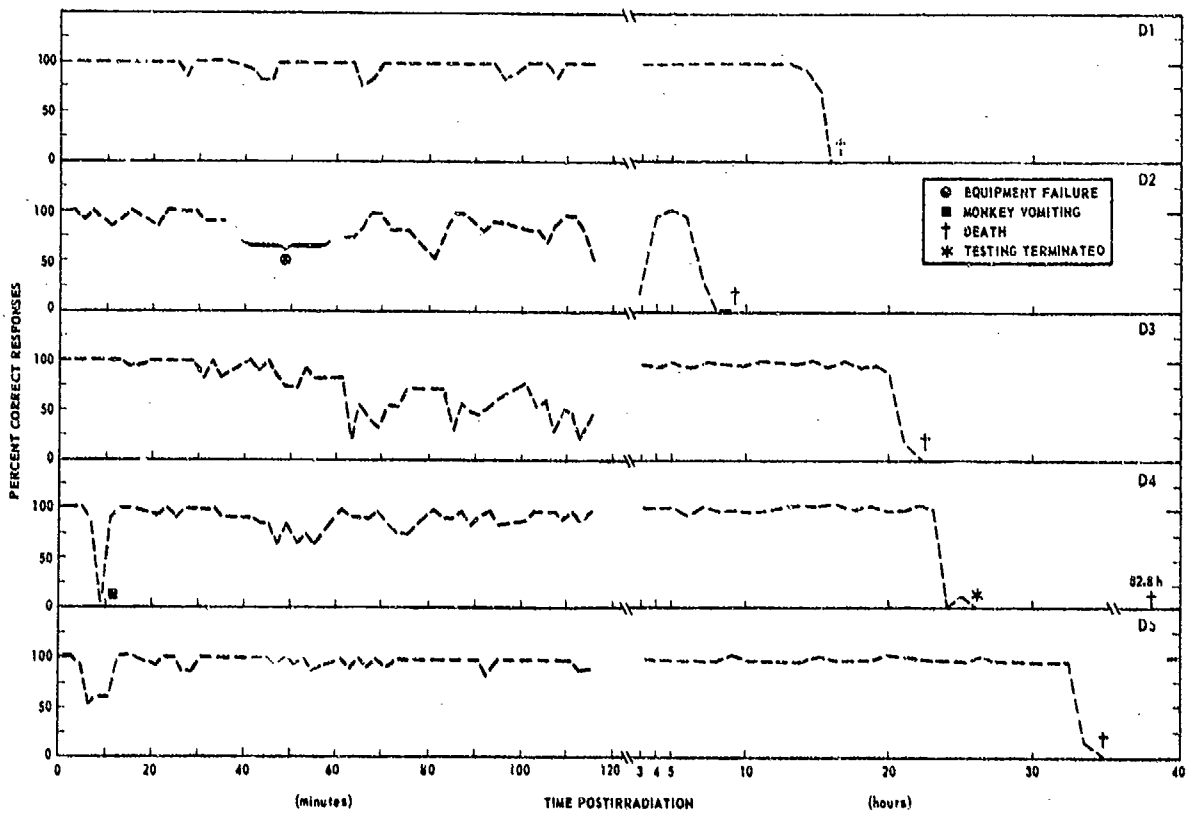

Figure 4. Performance of antihistamine-treated monkeys (20 mg chlorpheniramine preirradiation) following a 4000-rad dose of mixed gamma-neutron radiation. Approximately 8 minutes postirradiation, D4 was unable to operate the lever as vomitus on lever prevented accurate responses although he was performing correctly.

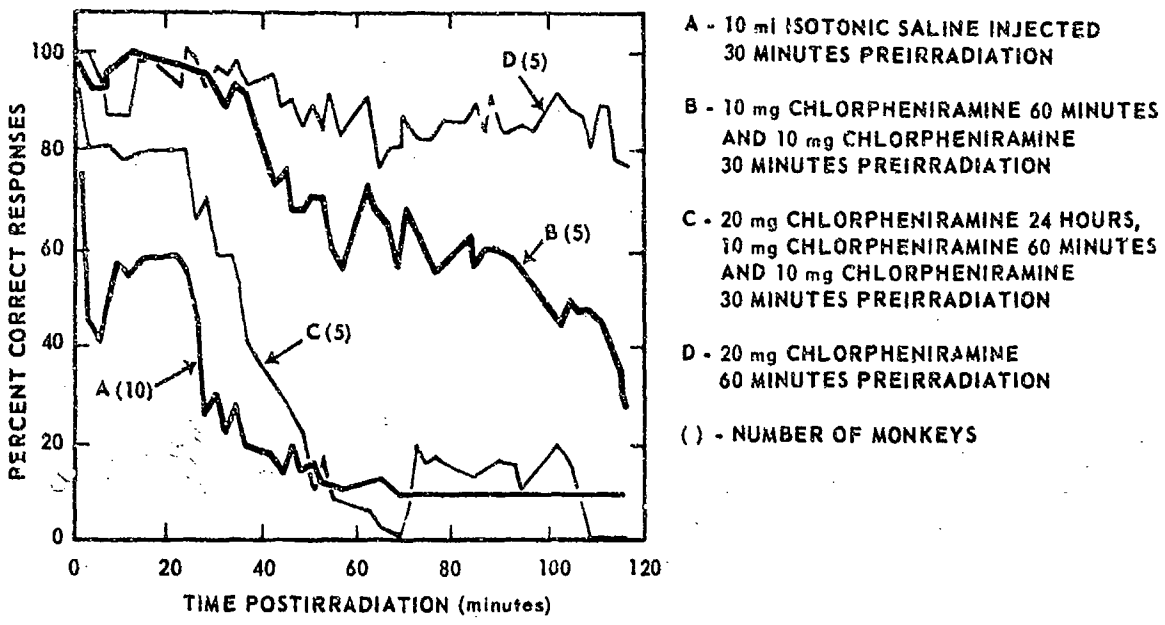

Figure 5. Average performance of saline- or chlorpheniramine-treated monkeys following a 4000-rad dose of mixed gamma-neutron radiation

Performance of the chlorpheniramine-treated monkeys of Groups B, C and D (Figure 5) was significantly better for the first 40 minutes postirradiation than that of the monkeys which received saline (Group A). After 44 minutes there was no significant difference in performance between the monkeys which received 40 mg of chlorpheniramine (Group C) during the 24 hours preirradiation and the saline-treated animals. The performance of the chlorpheniramine-treated monkeys of Groups B and D continued to be significantly better than the saline-treated monkeys (Group A) for the entire observation period. However, after 40 minutes postirradiation, the performance of Group B declined more rapidly than did the performance of group D. Although it is suggested that the difference is attributable to the effect of surgery, the somewhat different drug administration time may also have influenced the results.

The immediate postirradiation decline in blood pressure in the chlorpheniramine-treated monkeys (Figure 6) was not as severe as that of the saline-treated monkeys. However, the only group means that differed significantly were those of Groups A and B after 20 minutes postirradiation ($p < .05$, Student's "t" test).

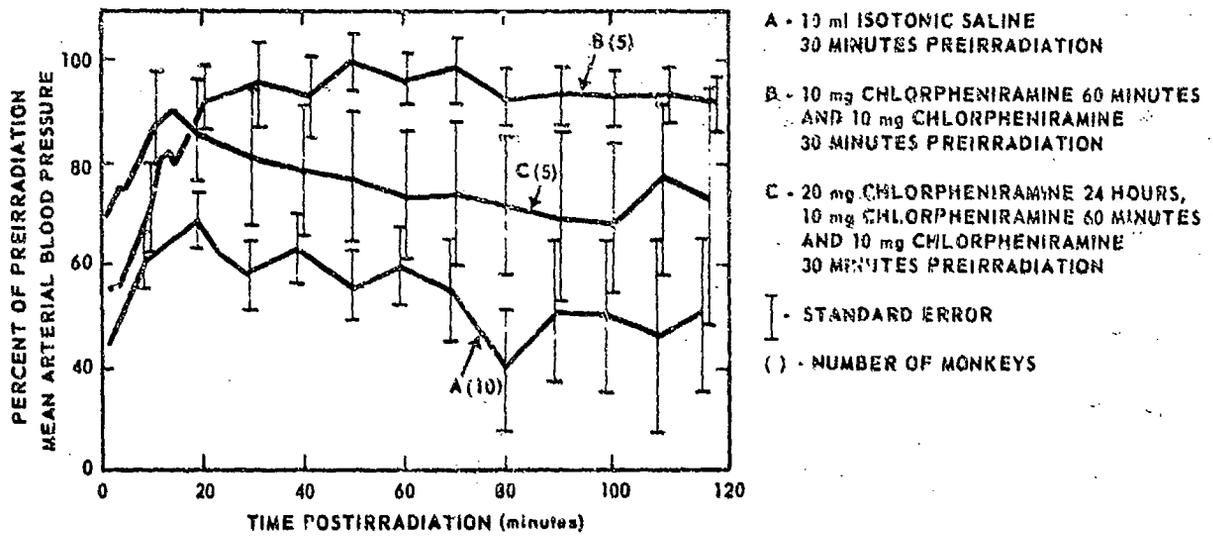

Figure 6. Mean arterial blood pressure of saline- or chlorpheniramine-treated monkeys following a 4000-rad dose of mixed gamma-neutron radiation

IV. DISCUSSION

The average blood pressures of the chlorpheniramine-treated groups were higher throughout the observation period than those of the saline-treated control group and were above what is considered a critical value (50 - 60 percent of the preirradiation mean arterial pressure) for adequate cerebral circulation.[2,5] Similar results have been reported previously in untrained, chlorpheniramine-treated monkeys.[4]

There was no correlation between the fall of mean arterial blood pressure and the occurrence of severe performance decrement. Some animals stopped performing

during the time that their blood pressure measurements were well above critical levels (Figures 1, 2 and 3). However, no animal with blood pressure below critical levels performed adequately for more than a few minutes.

The poorer performance of those animals which received chlorpheniramine on 2 consecutive days and were then irradiated may be explained by the fact that although the plasma half-life of chlorpheniramine (in the dog)[6,7] is only 3 hours, and its antihistaminic effects last only 4 to 6 hours,[3] the metabolites of chlorpheniramine have a half-life of approximately 10 days.[7] The performance decrement might be secondary to the toxic effects of metabolites of chlorpheniramine rather than to the histamine-antihistamine relationship of chlorpheniramine; however, there is no experimental evidence in support of this latter supposition.

V. CONCLUSIONS

The antihistamine chlorpheniramine maleate is effective in preventing ETI, postirradiation performance decrement, and in reducing the hypotension observed in monkeys after a 4000-rad dose of mixed gamma-neutron radiation. Since the major pharmacological effect of chlorpheniramine is blocking histamine receptor sites, its effectiveness in preventing or modifying the radiation-induced performance changes and hypotension can be taken as further evidence that histamine is involved in the acute radiation syndrome. However, the ETI-ameliorating properties of chlorpheniramine are not mediated through the maintenance of arterial blood pressure. An earlier study[9] in which similarly trained and irradiated monkeys were infused with norepinephrine so that blood pressure was maintained above 100 mm Hg did not differ significantly in performance from controls. Some mechanism other than deficient blood pressure, yet capable of being ameliorated by chlorpheniramine, is implicated in ETI.

REFERENCES

1. Black, J. W., Duncan, W. A. M., Durant, C. J., Ganellin, C. R. and Parsons, E. M. Definition and antagonism of histamine H_2-receptors. Nature 236:385-390, 1972.

2. Chapman, P. H. and Young, R. J. Effect of cobalt-60 gamma irradiation on blood pressure and cerebral blood flow in the Macaca mulatta. Radiation Res. 35:78-85, 1968.

3. Douglas, W. W. Histamine and antihistamines; 5-hydroxytryptamine and antagonists. In: The Pharmacological Basis of Therapeutics, 4th ed., Goodman, L. S. and Gilman, A., editors, pp. 621-662. New York, N.Y., The Macmillan Company, 1970.

4. Doyle, T. F., Turns, J. E. and Strike, T. A. Effect of antihistamine on early transient incapacitation of monkeys subjected to 4000 rads of mixed gamma-neutron radiation. Aerospace Med. 42:400-403, 1971.

5. Finnerty, F. A., Jr., Witkin, L. and Fazekas, J. F. Cerebral hemodynamics during cerebral ischemia induced by acute hypotension. J. Clin. Invest. 33:1227-1232, 1954.

6. Kamm, J. J., Ferullo, C. R., Miller, D. and Van Loon, E. J. Metabolism of chlorpheniramine-^{3}H by the rat and dog. Biochem. Pharmacol. 18:659-671, 1969.

7. Peets, E. A., Weinstein, R., Billard, W. and Symchowicz, S. The metabolism of chlorpheniramine maleate in the dog and rat. Arch. Int. Pharmacodyn. 199: 172-190, 1972.

8. Thorp, J. W. and Young, R. W. Monkey performance after partial body irradiation. Aerospace Med. 42:503-507, 1971.

9. Turns, J. E., Doyle, T. F. and Curran, C. R. Norepinephrine effects on early postirradiation performance decrement in the monkey. Bethesda, Maryland, Armed Forces Radiobiology Research Institute Scientific Report SR71-16, 1971.