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The Prevention of Radiation-Induced, Early, Transient Incapacitation of Monkeys by an Antihistamine (37945)

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(Introduced by T. A. Strike)

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Immediately following large, supralethal doses of ionizing radiation, monkeys usually show a performance decrement the severity of which is dose related (1). Generally, the performance decrement of monkeys exposed to a 4-krad dose of mixed gamma–neutron radiation starts as early as 2 min after irradiation and lasts for 10–30 min 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% of normal (2).

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 (3, 4), 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.

Materials and Methods. The animals used were 2- to 3-year-old male monkeys (*Macaca mulatta*) weighing 3–5 kg. The care and maintenance of these monkeys have been described elsewhere (1, 2).

Each monkey was trained to perform a discrete trial, cued avoidance task. At the beginning of each trial, a 1-sec warning tone and a 5.5-sec 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 sec of the trial, a 0.5-sec electrical shock was administered to the monkey's tail. The shock and light terminated simultaneously and a 4.5-sec 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 sec. If the animal moved the correct lever within the first 5 sec 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% of the time, to 2000 consecutive trials.

Twenty-five trained monkeys were divided into four experimental groups, as indicated below. The monkeys in 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. These catheters were used for recording blood pressure and administering drugs. Clotting of the catheters was pre-

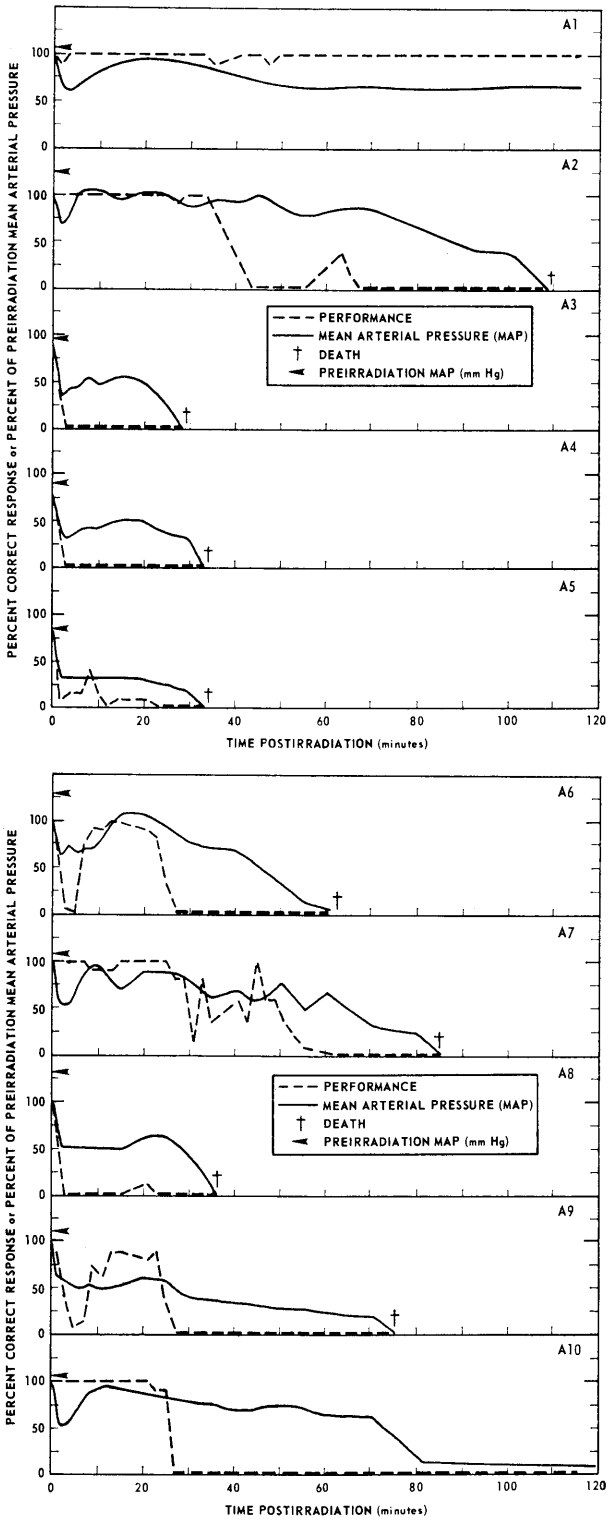

FIG. 1. Performance and mean arterial blood pressure of saline-treated monkeys following a 4000-rad dose of mixed gamma–neutron radiation.

vented by refilling them with a 1% 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 min before irradiation and served as the control group.

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

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

All monkeys were given a 100-trial performance test beginning 25 min 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 sec after the pulse. Each test period (block) consisted of 100 trials. The performance testing of all monkeys was continued for 2 hr after irradiation unless death intervened. During this time they were

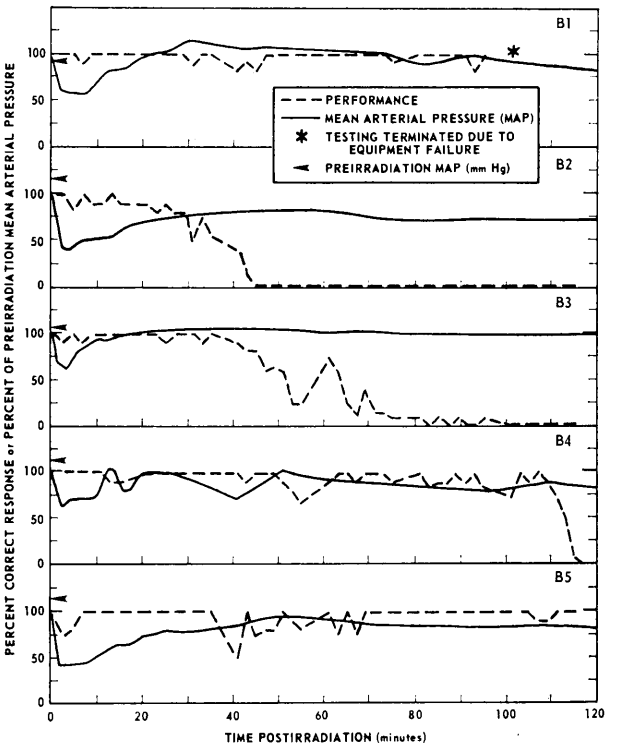

FIG. 2. Performance and mean arterial blood pressure of antihistamine-treated monkeys (10 mg chlorpheniramine 60 min and 10 mg chlorpheniramine 30 min preirradiation) following a 4000-rad dose of mixed gamma–neutron radiation.

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-min interval (10 trials) was calculated and plotted at the midpoint of that interval. After each block of 100 trials, there was a 3.4-min rest period. Following the initial 2-hr 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% correct response. Performance less than 90% correct was considered a performance decrement.

Early transient incapacitation (ETI). Failure to respond for four or more consecutive trials during the first 30 min 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.

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

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

Performance of the chlorpheniramine-treated monkeys of Groups B, C, and D (Fig. 5) was significantly better for the first 40 min postirradiation than that of the monkeys which received saline (Group A).

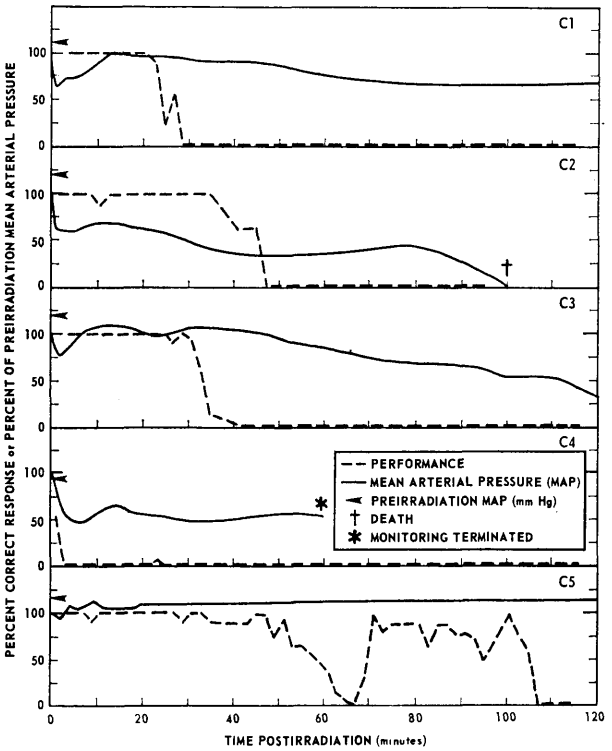

FIG. 3. Performance and mean arterial blood pressure of antihistamine-treated monkeys (20 mg chlorpheniramine 24 hr, 10 mg chlorpheniramine 60 min, and 10 mg chlorpheniramine 30 min preirradiation) following a 4000-rad dose of mixed gamma–neutron radiation.

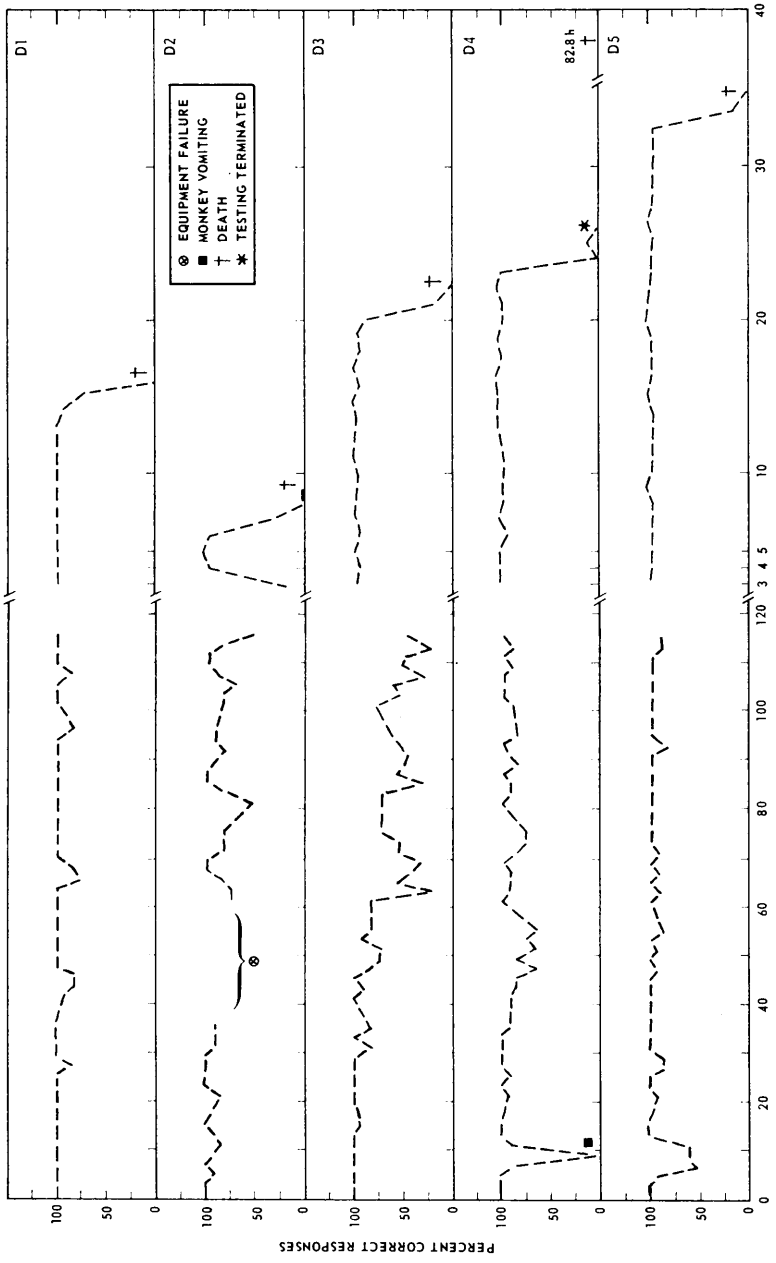

FIG. 4. Performance of antihistamine-treated monkeys (20 mg chlorpheniramine preirradiation) following a 4000-rad dose of mixed gamma–neutron radiation. Approximately 8 min postirradiation, D4 was unable to operate the lever as vomitus on lever prevented accurate responses although he was performing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

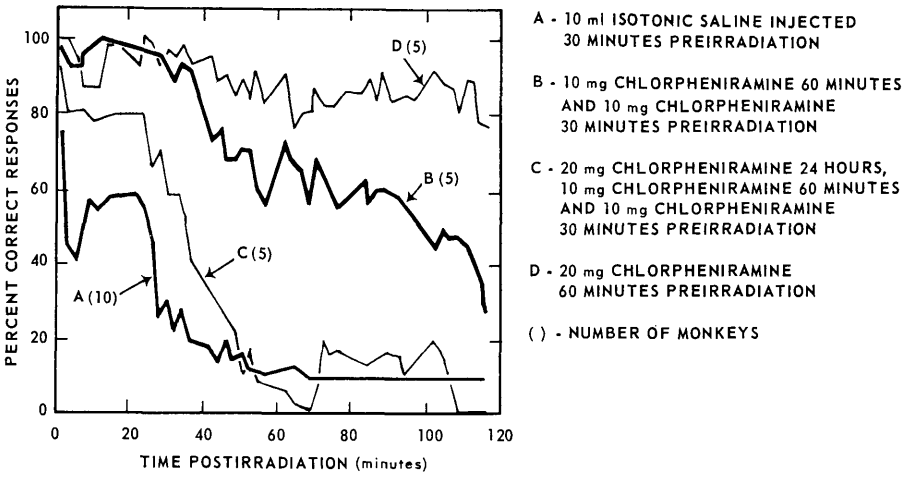

FIG. 5. Average performance of saline- or chlorpheniramine-treated monkeys following a 4000-rad dose of mixed gamma–neutron radiation.

After 44 min there was no significant difference in performance between the monkeys which received 40 mg of chlorpheniramine (Group C) during the 24 hr 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 min postirradiation, the performance of Group B declined more rapidly than did the performance of Group D.

The immediate postirradiation decline in blood pressure in the chlorpheniramine-treated monkeys (Fig. 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 min postirradiation ($P < .05$, Student's t test).

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% of the preirradiation mean arterial pressure) for adequate

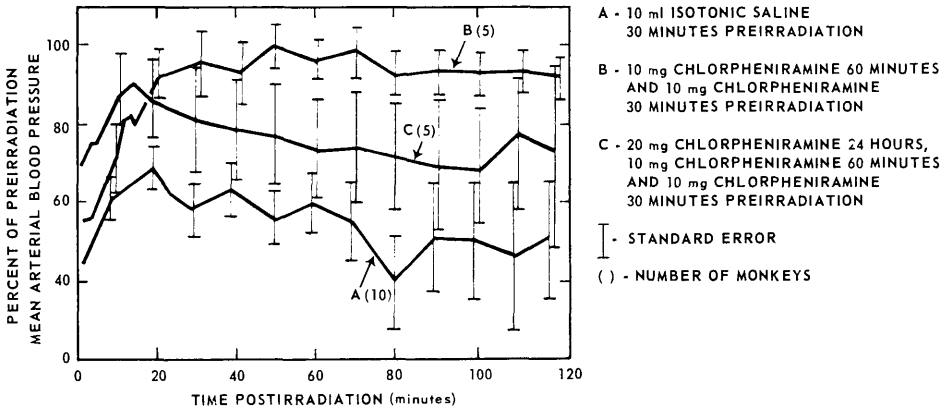

FIG. 6. Mean arterial blood pressure of saline- or chlorpheniramine-treated monkeys following a 4000-rad dose of mixed gamma–neutron radiation.

cerebral circulation (5, 6). Similar results have been reported previously in untrained, chlorpheniramine-treated monkeys (2).

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 (Figs. 1–3). However, no animal with blood pressure below critical levels performed adequately for more than a few minutes.

The absence of any enhanced effect on performance of two consecutive days treatment with chlorpheniramine may be attributed to the short (3 hr in the dog) half-life (7, 8) and an antihistaminic effect lasting 4–6 hr (4). The antihistaminic effect of the first dose would have dissipated by the time the second dose was given 24 hr later. The reason for the poorer performance following the second dose of chlorpheniramine is unclear. It is possible that the metabolites of chlorpheniramine, which have a half-life of approximately 10 days (8), interfere in some way with the binding of chlorpheniramine at the histamine receptor sites, rendering the second dose less effective as an antihistamine. It is also possible that the side effects, drowsiness for example, of this antihistamine or its metabolites are cumulative and interfere with performance outside of the histamine–antihistamine relationship.

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 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 similarity trained and irradiated monkeys were infused with norepinephrine so that blood pressure was maintained above 100 mm Hg did not show significant differences in performance from controls. Some mechanism other than deficient blood pressure, yet capable of being ameliorated by chlorpheniramine, is implicated in ETI.

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