Radioprotective Effect of Magnesium Pemoline: A Comparison with Pemoline and Dextroamphetamine

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Magnesium pemoline, a central nervous system stimulant, is found to have a significant protective effect against ionizing radiations. Experimental results show that this drug is more potent than pemoline alone in exhibiting this radioprotective effect, and that dextroamphetamine does not possess this property. It is suggested that magnesium hydroxide, a component of magnesium pemoline, might enhance the absorption of pemoline to produce a more significant effect than when pemoline alone [without $Mg(OH)_2$] is used. The mechanism of this phenomenon is discussed, but no explanations are offered.

RECENTLY the authors reported the protective effect of magnesium pemoline against lethal doses of X-irradiations (1). Mice injected intraperitoneally with this drug showed a significant higher percentage of survival when exposed whole body to a total dose of 900 rads when compared with those injected with tragacanth. Further experiments were designed to compare the radioprotective effect of magnesium pemoline, of pemoline alone, and also that of another central nervous system stimulant, dextroamphetamine. Results of these studies are described and discussed in this paper.

METHOD

During the initial investigations, the experiments were designed to test the effect of magnesium pemoline on conditioned avoidance response in mice using X-rays as an unconditioned stimulus. Radioprotective effect of this drug was accidentally observed during these studies. Since then the experimental design has been changed to suit new objectives, although the same techniques were used in injecting and irradiating the animals.

Again CF_1 male mice (20–22 Gm.), 50 to 60 days old were used. The animals divided into five groups of 60 mice each were housed in standard plastic cages, 10 animals per cage. There was no restriction on food and water. On the first day of the experiment, 1 week after their arrival from the supplier, the mice in the first group were injected intraperitoneally with 0.6 ml. of magnesium pemoline (at a dose of 70 mg./Kg.), the second group with dextroamphetamine (0.7 mg./Kg.), the third group with pemoline alone (55 mg./Kg.), the fourth group with bacteriostatic water (0.3% tragacanth), and the fifth group with magnesium hydroxide, a component of magnesium pemoline (18 mg./Kg.). Magnesium pemoline, dextroamphetamine, pemoline, and magnesium hydroxide solutions were prepared with 0.3% tragacanth. All the mice were then exposed to 750 rads (at 80 rads/min.) of X-irradiations immediately after injection. A 400 Kv. Maxitron X-ray machine served as the source of radiation. The animals were then removed from the radiation room and returned to their original cages. Mortality in each group was observed and recorded daily. The experiments were repeated for three consecutive times. Data gathered from each group were then averaged each time and standard deviations obtained for all three experimental runs. Thus a total of 900 mice was used during this experiment.

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RESULTS AND DISCUSSION

As can be seen from Table I, the group injected with magnesium pemoline immediately before exposure to X-irradiation resisted against radiations longer than any of the other four groups. Comparing the magnesium pemoline group and the control group injected with tragacanth, one observes that this drug not only protects the animals against radiations (35% survival after 30 days) but also delays the damaging effect of radiation (100% survival on the seventh postirradiation day *versus* 79% in the control group). The rate of mortality was much less pronounced. On the thirteenth day after exposure while all the animals in the control group had died, 54% of the magnesium pemoline group still survived. Most of the mice in all groups died within the second postirradiation week. For the group treated with pemoline only, the delaying protective effect was not quite as significant when compared to the control (tragacanth) group. Nevertheless, 30-day mortality observation showed 15% of this group still survived, and at the end of the second week after exposure, 31% of the mice in this group were still alive *versus* 0% for the control group. Dextroamphetamine did not exhibit any protective effect against radiations. There was no significant difference between the mortality in this group and that in the control group. Magnesium pemoline is composed of 75 wt. % of pemoline and 25 wt. % of magnesium hydroxide. Table I also shows that the mice injected with $Mg(OH)_2$ died as fast as those in the control group and none survived 14 days after being exposed to lethal doses of ionizing radiations.

Comparing the radioprotective effect of magnesium pemoline and pemoline alone, one notes that the latter also offers protection but not as effectively as the former. On the eighth postirradiation day, the difference between the survival percentage of these two groups was quite significant ($p \ll 0.001$). Two weeks after exposure, this level of significance was still quite considerable ($0.05 < p < 0.02$). After 30 days while 15% of the animals in pemoline group survived, 35% were still alive in the magnesium pemoline group. Plotnikoff and Meekma (2) reported that magnesium pemoline was more potent in enhancing acquisition and retention of memory than pemoline alone, and that $Mg(OH)_2$ showed no significant effects. The results confirmed these findings as far as radioprotective effect of this drug was concerned. Comparing the doses used by these investigators and that used in these experi-

TABLE I—PERCENTAGE OF SURVIVAL OF 5 GROUPS OF MICE INJECTED WITH MAGNESIUM PEMOLINE, TRAGACANTH, $Mg(OH)_2$, DEXTROAMPHETAMINE, AND PEMOLINE, AND EXPOSED TO 750 RADS

Post-irradiation Days	Magnesium Pemoline	Tragacanth	$Mg(OH_2)$	Dextroamphetamine	Pemoline
1	100 ± 0	100 ± 0	100 ± 0	100 ± 0	100 ± 0
2	100 ± 0	100 ± 0	100 ± 0	100 ± 0	100 ± 0
3	100 ± 0	100 ± 0	100 ± 0	100 ± 0	100 ± 0
4	100 ± 0	100 ± 0	100 ± 0	100 ± 0	100 ± 0
5	100 ± 0	100 ± 0	98 ± 0.3	100 ± 0	98 ± 1.0
6	100 ± 0	94 ± 1.3	92 ± 0.7	87 ± 3.3	87 ± 1.5
7	100 ± 0	79 ± 2.9	79 ± 3.2	76 ± 3.5	75 ± 2.9
8	97 ± 1.2	57 ± 3.6	58 ± 2.6	52 ± 3.2	70 ± 0.2
9	94 ± 0.5	44 ± 2.5	48 ± 1.7	36 ± 1.6	64 ± 3.3
10	80 ± 2.6	24 ± 1.8	32 ± 1.7	29 ± 0.3	62 ± 1.1
11	69 ± 3.9	12 ± 2.4	25 ± 0.9	17 ± 2.5	54 ± 2.6
12	62 ± 0.2	7 ± 1.8	12 ± 1.3	8 ± 1.3	50 ± 1.7
13	54 ± 3.1	3 ± 0.5	9 ± 0.2	5 ± 0.2	40 ± 2.0
14	47 ± 1.5	0	6 ± 0.3	4 ± 0.1	31 ± 1.5
15	45 ± 0.2		0	0	29 ± 0.6
16	40 ± 1.1				25 ± 0.3
17	37 ± 0.6				20 ± 1.2
18	37 ± 0.6				15 ± 1.3
19	35 ± 0.3				15
20	35				15
21	35				15
22	35				15
23	35				15
24	35				15
25	35				15
26	35				15
27	35				15
28	35				15
29	35				15
30	35				15

ments, our dose was much higher (70 mg./Kg. *versus* 1.25–5.0 mg./Kg.). The authors are in the process of studying this radioprotective effect at lower doses of magnesium pemoline and higher doses of pemoline alone. It has been generally suggested that magnesium hydroxide serves as a carrier for pemoline, thus the magnesium hydroxide component enhances the absorption of this drug. If this is the case, perhaps one could verify this by increasing the amount of pemoline in order to compensate for the slower rate of absorption when only pemoline is used. In any case, pemoline alone was responsible for the protection against lethal doses of radiation. So far, no pharmacological findings have offered any clues that could be used to explain this phenomenon. Lange *et al.* (3) have observed significant anticonvulsant activity 15 to 30 min. after oral administration of magnesium pemoline (100 mg./Kg.) and 60 min. after the administration of pemoline alone of the same dose. This delayed effect of pemoline without magnesium hydroxide seems to agree with the less radioprotective effectiveness in these experiments; however whether one can associate these findings with Lange's observations is still a question for further investigations. Furthermore, if this suggestion is true it would be difficult to explain the long-term protective effect of magnesium pemoline against ionizing radiations that we have observed.

SUMMARY

The following observations resulted from this study: (*a*) Radioprotective effect of both magnesium pemoline and pemoline alone are quite significant. (*b*) Magnesium pemoline is more potent than pemoline alone in exhibiting protective effect against ionizing radiation. (*c*) Dextroamphetamine does not possess this radioprotective effect. (*d*) Magnesium hydroxide, a component of magnesium pemoline, seems to enhance the absorption rate of pemoline in this effect.

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Keyphrases

Radiation protective agent
Magnesium pemoline—radioprotective effect
X-Irradiation exposure—mice