probably 4-H of ring, 1H) p.p.m. (each J_{4-5} = 5.7 c.p.s. ± 0.2 c.p.s.).

The NMR spectrum of VI in deuterated chloroform was δ = 3.58 (t, probably C—CH_2—Cl, 4H), 4.08 (t, probably N—CH_2—C, 4H), 4.38 (s, thienyl—CH_2—N, 2H), and 7.54 (s, 4-H of ring, 1H) p.p.m.

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Pemoline and Magnesium Hydroxide *Versus* Pemoline: Enhancement of Learning and Memory of a Conditioned Avoidance Response in Rats

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Pemoline and magnesium hydroxide was found to be several times more potent than pemoline in enhancing the acquisition and retention of a conditioned avoidance response in rats.

NUMEROUS STUDIES in Europe indicated that the performance of fatigued humans was enhanced by pemoline under various test conditions (1–3). In previous studies Plotnikoff (4–7) reported that pemoline and magnesium hydroxide (PMH)[1] enhanced the acquisition and retention of a conditioned avoidance response in rats. The present study is a comparative study of PMH and pemoline on the same avoidance response.

EXPERIMENTAL

Methods—The test chamber as well as rates of acquisition and retention used for all conditioning studies were described earlier (4–7). The test equipment consisted of a wood chamber (11 × 12 in.) with a grid flooring. An escape platform was placed 11 in. above the grid floor outside of the test chamber. Male Sprague-Dawley rats (170 to 220 Gm.) were used. Only "slow learners" were used for all drug studies. Suspensions of the test drugs were prepared in 0.3% tragacanth. Acquisition trials consisted of the following 30-sec. sequence: 15 sec. inside the chamber without shock or buzzer, 10 sec. with buzzer, and finally 5 sec. of shock with buzzer. Retention trials consisted of a 30-sec. sequence without buzzer or shock stimulation. Criterion of learning was considered obtained when the mean jump-out time was 15 sec. or less for any given trial and succeeding trials.

Results—The principal difference observed between pemoline and PMH on the jump-out test was one of potency. As the data in Tables I and II illustrate, PMH is more potent in the enhancement of acquisition and retention of the jump-out response. In several studies, significant enhancement was observed with 0.3% tragacanth suspensions of PMH at doses of 1.25, 2.5, and 5.0 mg./Kg. p.o. In contrast, pemoline (0.3% tragacanth suspension) only showed significant enhancement at doses of 10 and 20 mg./Kg. p.o. Lower doses of pemoline (2.5 and 5.0 mg./Kg. p.o.) did not enhance acquisition or retention.

The approximate potency differences on acquisition between the two compounds is at least eightfold. Rats treated with PMH reached criterion of learning by the 9th trial at a dose of 1.25 mg./Kg., whereas pemoline-treated rats reached criterion of learning by the 4th trial at a dose of 10 mg./Kg.

The potency differences between the two compounds on retention were also approximately eightfold (1.25 mg./Kg. *versus* 10.0 mg./Kg.). Significant retention of the jump-out response was observed at a dose of 1.25 mg./Kg. in PMH-treated animals, whereas pemoline-treated animals only showed significant retention at a dose of 10 mg./Kg.

Control studies carried out with $Mg(OH)_2$ indicated there were no significant effects on acquisition or retention.

DISCUSSION

The present study has demonstrated that PMH is a more potent agent in enhancing acquisition and retention than pemoline. A similar difference between pemoline and PMH has been reported by Lange *et al.* (8) on anticonvulsant activity. The principal difference reported was the rate of absorption as determined by onset of anticonvulsant activity. PMH at a dose of 100 mg./Kg. exerted significant activity 15–30 min. after oral administration, whereas pemoline at the same dose exhibited activity only at 60 min. However, both PMH and pemoline have the same LD_{50} values in mice (oral LD_{50} 500 mg./Kg.). The effects of the two compounds are both similar resulting in overt stimulant effects at doses of 5–400 mg./Kg. and paradoxical depression (ataxia followed by coma) at toxic doses (500–1000 mg./Kg.). No convulsions were observed at toxic doses.

In the present study, PMH was demonstrated to be a more potent agent than pemoline in enhancing acquisition and, even more striking, retention of the jump response. Thus, it is possible that magnesium hydroxide component may be enhancing absorption. Clinically (9) PMH has been reported to have a faster onset of action and to have greater potency as an arousal agent than pemoline.

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[1] Marketed as Cylert by Abbott Laboratories, North Chicago, Ill. Abbott-30400; an equimolar combination of 2-imino-5-phenyl-4-oxazolidinone (Abbott-13397) and magnesium hydroxide.

TABLE I—EFFECT OF PMH ON THE ACQUISITION AND RETENTION OF THE JUMP-OUT RESPONSE (ORAL ROUTE)

Trial	Dose, mg./Kg.	Acquisition, Day 1	Retention, Day 2
1	1.25	30.0 ± 0.0[a]	7.0 ± 1.7[b]
2		29.3 ± 0.7	7.3 ± 1.7
3		29.0 ± 0.4	8.0 ± 1.9
4		21.0 ± 3.4	6.7 ± 1.2
5		18.8 ± 4.3	5.5 ± 0.8
6		16.7 ± 4.1	6.0 ± 1.3
7		16.7 ± 4.1	6.3 ± 1.1
8		16.2 ± 3.8	6.3 ± 0.9
9		9.0 ± 0.9[b]	5.7 ± 1.4
10		6.8 ± 1.4[b]	6.2 ± 1.1
1	2.5	29.8 ± 0.2	8.3 ± 3.4[b]
2		29.5 ± 0.2	8.2 ± 3.6
3		18.3 ± 3.9	7.2 ± 1.4
4		15.8 ± 3.9	6.8 ± 1.9
5		15.0 ± 4.4	6.3 ± 1.5
6		13.2 ± 3.1	6.7 ± 1.1
7		11.7 ± 3.4	6.3 ± 1.2
8		10.5 ± 2.1[b]	6.3 ± 0.4
9		8.2 ± 2.1[b]	6.2 ± 0.8
10		9.3 ± 3.0[b]	6.5 ± 0.4
1	5.0	29.2 ± 0.3	8.5 ± 2.9[b]
2		26.7 ± 2.0	5.7 ± 1.1
3		21.3 ± 2.8	3.8 ± 1.1
4		18.3 ± 3.5	4.2 ± 0.9
5		12.0 ± 3.4	3.3 ± 0.9
6		11.0 ± 3.5	4.5 ± 0.8
7		13.0 ± 2.5	4.7 ± 0.8
8		11.7 ± 3.3[b]	5.3 ± 1.1
9		9.8 ± 2.0[b]	5.0 ± 1.6
10		6.3 ± 2.2[b]	5.0 ± 1.3
1	Controls	29.8 ± 0.2	19.5 ± 3.2
2		29.3 ± 0.4	19.0 ± 3.1
3		25.8 ± 2.6	17.8 ± 2.6
4		22.2 ± 2.7	17.8 ± 2.9
5		21.0 ± 3.1	19.3 ± 3.5
6		18.5 ± 2.8	19.3 ± 3.6
7		19.3 ± 2.3	20.1 ± 3.4
8		21.5 ± 2.5	21.7 ± 3.3
9		20.8 ± 1.8	23.5 ± 3.2
10		21.7 ± 2.8	21.8 ± 3.8

[a] Mean jump-out time in seconds of six rats ± S.E.
[b] Mean jump-out time significantly different from controls p 0.05 (10).

TABLE II—EFFECT OF PEMOLINE ON THE ACQUISITION AND RETENTION OF THE JUMP-OUT RESPONSE (ORAL ROUTE)

Trial	Dose, mg./Kg.	Acquisition, Day 1	Retention, Day 2
1	2.5	28.7 ± 0.4[a]	24.2 ± 3.7
2		20.7 ± 2.6	27.3 ± 2.3
3		13.8 ± 3.9	25.8 ± 3.6
4		14.3 ± 2.9	25.8 ± 3.8
5		19.0 ± 1.7	27.3 ± 2.7
6		16.5 ± 0.2	27.7 ± 2.3
7		17.7 ± 1.7	27.7 ± 2.3
8		17.3 ± 0.8	27.5 ± 2.5
9		17.0 ± 2.2	27.2 ± 2.8
10		16.0 ± 2.4	27.7 ± 2.3
1	5.0	28.3 ± 0.6	21.6 ± 4.0
2		23.7 ± 4.0	19.7 ± 4.3
3		13.0 ± 3.3	19.8 ± 4.4
4		13.7 ± 3.4	19.5 ± 4.0
5		13.8 ± 3.3	19.2 ± 4.0
6		13.0 ± 2.9	18.7 ± 4.1
7		12.5 ± 2.7	20.0 ± 4.5
8		12.3 ± 2.6	20.0 ± 4.4
9		16.3 ± 3.5	17.2 ± 4.3
10		16.8 ± 3.7	20.0 ± 4.8
1	10.0	28.0 ± 0.6	6.5 ± 1.7[b]
2		23.0 ± 2.6	8.3 ± 2.1
3		18.5 ± 4.2	7.3 ± 1.9
4		8.8 ± 2.7[b]	5.3 ± 0.8
5		7.3 ± 1.9	6.0 ± 1.2
6		8.8 ± 2.5	4.5 ± 1.0
7		4.7 ± 0.8	4.0 ± 1.3
8		5.2 ± 1.7	4.0 ± 1.2
9		4.8 ± 1.3	4.0 ± 1.4
10		3.0 ± 0.6	4.7 ± 0.8
1	Controls	28.0 ± 0.5	18.2 ± 3.6
2		21.7 ± 3.0	17.2 ± 2.4
3		19.0 ± 3.4	17.3 ± 2.0
4		18.5 ± 3.0	20.0 ± 2.4
5		16.7 ± 3.2	18.7 ± 2.5
6		20.3 ± 3.6	18.8 ± 2.4
7		17.0 ± 3.3	21.3 ± 3.4
8		17.3 ± 2.8	22.8 ± 3.5
9		16.3 ± 2.0	23.5 ± 3.8
10		14.2 ± 1.2	23.5 ± 2.8

[a] Mean jump-out time in seconds of six rats ± S.E.
[b] Mean jump-out time significantly different from controls p 0.05 (8).

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