ANTAZOLINE HYDROCHLORIDE, TRIPELENNAMINE HYDROCHLORIDE AND LOCOMOTOR ACTIVITY

By James A. Baird and Eldon M. Boyd

From the Department of Pharmacology, Queen's University, Kingston, Ontario, Canada

Received January 14, 1954

The lack of effect of bromazine hydrochloride, in oral and subcutaneous doses up to 200 mg./kg. body weight, upon locomotor activity was reported in a previous communication by Baird and Boyd[1]. An investigation of a similar nature has been made upon two other antihistamine agents, tripelennamine hydrochloride and antazoline hydrochloride. The results of this investigation are reported below. Antazoline hydrochloride was found to depress locomotor activity over a wide range of doses while tripelennamine hydrochloride was without statistically significant effect upon this measurement of complex, co-ordinated reflex action, in doses up to those which produced toxic effects and death.

Quantitative pharmacological evaluation of "sedative" activity is usually made by some form of titration of the action of a sedative drug against a challenging stimulation of the central nervous system by physical or chemical agents (e.g., Chen and Portman[2]). Swinyard, Jolley and Goodman[3] have reported that tripelennamine hydrochloride accentuates leptazol convulsions and modifies electro-shock convulsions in albino rats. Evaluation of sedative or excitant activity may be made also by a quantitative record of signs and symptoms. Kutscher and Chilton[4] recorded that therapeutic doses of tripelennamine hydrochloride did not affect pain threshold as measured by the Hardy-Wolff-Goodell apparatus. Boyd and Boyd[5], and Boyd, Boyd and Cassell[6] have measured quantatively the sedative and excitant properties of various antihistamine agents upon dogs. Since locomotor activity can be readily measured upon albino rats it was decided to determine this as a gauge of the sedative or excitant effects of tripelennamine hydrochloride and of antazoline hydrochloride.

Method

Locomotor activity was measured on albino rats assembled in Wahmann vertically-revolving drums by the method of Griffith and Farris[7] as adapted by Baird and Boyd[1]. These activity wheels have been extensively employed in psychological laboratories for many years (e.g., Shirley[8] and Skinner[9]). The albino rats were young healthy adults from a colony which has been maintained in the animal quarters of this department at Queen's University since 1937. They were fed a proprietary "checkers" diet and water *ad libitum*. Approximately equal numbers of male and female rats were used in each experiment.

Locomotor activity sufficient to cause rotation of the drum was recorded by a Veeder counter. The work required to make one revolution of

each drum was measured and this measurement, in ergs, repeated at intervals of 1 to 2 months as a check upon the efficiency of the drums. The locomotor activity of each rat was measured at intervals of 1 hour by recording the number of revolutions of the drum during that interval. The results were expressed as revolution per rat per hour. Hourly readings were taken for 3 hours before and 4 hours after the administration of a drug or control solution.

To measure the effect upon locomotor activity of an established sedative drug, 50 albino rats were divided into 2 groups of 25 animals each and given barbital sodium orally in doses of 5·0 and 10·0 mg./kg. body weight respectively. The animals were used in rotation as controls or barbital-treated, the same numbers of each being measured together at weekly intervals. The mean locomotor activities are shown in Table I. Barbital sodium in these doses, which correspond on a body weight basis to the administration of 1 and 2 tablets of 0·3 g. each to an average man, produced sedation of locomotor activity which, over the 4 hours, averaged 35 and 41 per cent. decline respectively.

TABLE I

THE EFFECT OF ORAL ADMINISTRATION OF BARBITAL SODIUM UPON THE LOCOMOTOR ACTIVITY OF ALBINO RATS

Dose of barbital sodium (mg./kg.)	Number of animals	Mean locomotor activity (revolutions per rat per hour)			
		1st hour	2nd hour	3rd hour	4th hour
0 (control)	25	36	38	53	46
5	25	23	23	35	32
0 (control)	25	79	89	73	47
10	25	42	35	47	46

The effect of tripelennamine hydrochloride was determined upon a group of 25 albino rats. The animals were divided into sub-groups of 5 and given by subcutaneous injection at intervals of 1 week, in rotation until cross-over was complete, 0, 1·0, 5·0, 10 and 25 mg./kg. body weight of tripelennamine hydrochloride dissolved in 1 ml./kg. body weight of distilled water.

Within 2 days after injection of the 2 larger doses of tripelennamine hydrochloride, there appeared a swelling at the site of injection which progressed to ulcer formation in the number of albino rats noted in Table II. Healing of the ulcers was complete by the 10th to 14th days. Such ulcers have been reported previously by Mayer, Hays, Brousseau, Mathieson, Rennick and Yonkman[10]. The mean locomotor activities of albino rats with ulcers of 1 week's standing were 41 $\pm$ 6 revolutions per rat per hour, while activities of the same rats just before injection of the ulcer-producing agent were 39 $\pm$ 9 revolutions per rat per hour. Thus, the presence of a week-old ulcer had no effect upon locomotor activity and such rats were retained in the rotation schedule.

To ascertain the effect upon locomotor activity of higher doses of tripelennamine hydrochloride, a second group of 25 albino rats was

divided into 5 sub-groups of 5 animals each. Animals of each sub-group were given orally 0, 25, 100 and 200 mg./kg. body weight of tripelennamine hydrochloride in rotation at intervals of 1 week. Omitted from the series at each rotation was 1 sub-group originally scheduled to receive a higher dose of the antihistamine agent. The 200 mg./kg. dose killed 20 per cent. of the albino rats. Interest in this study was not in the effect of toxic doses, which have been described by Mayer, Hays, Brousseau, Mathieson, Rennick and Yonkman[10].

TABLE II

THE INCIDENCE OF ULCER FORMATION AT THE SITE OF SUBCUTANEOUS INJECTION OF TRIPELENNAMINE HYDROCHLORIDE AND OF ANTAZOLINE HYDROCHLORIDE IN ALBINO RATS

Dose of antihistamine drug (mg./kg.)	Concentration injected per cent.	Incidence of ulcer formation (per cent. of 25 animals)	
		Tripelennamine hydrochloride	Antazoline hydrochloride
0·0	0·00	0	0
1·0	0·10	0	—
2·0	0·20	—	0
5·0	0·50	0	—
10·0	1·00	88	0
20·0	2·00	—	76
25·0	2·50	96	—
50·0	5·00	—	92

Experiments similar to those upon tripelennamine hydrochloride were performed upon 2 groups of 25 albino rats each, using antazoline hydrochloride. The 5-rat sub-groups of the first 25 rats received subcutaneously 0, 2·0, 10, 20 and 50 mg./kg. body weight of antazoline hydrochloride respectively, weekly and in rotation until cross-over was complete. Ulcers at the site of injection appeared at the frequencies summarised in Table II and have been previously reported by Schindler[11]. 4 of the sub-groups of the second 25 rats were given orally 0, 25, 100 and 200 mg./kg. body weight of antazoline hydrochloride in rotation until cross-over was complete. The fifth sub-group was given increasing doses of 300, 400, 500 and 750 mg./kg. body weight, each dose given once only to 5 rats. The largest dose killed 80 per cent. of the rats.

RESULTS

Tripelennamine hydrochloride had a statistically insignificant effect upon locomotor activity. There was some indication from the data that the locomotor activity of the more active rats might be increased by the smaller doses, and decreased by the larger doses, of tripelennamine hydrochloride. There was also some indication that the locomotor activity of the less active rats might be augmented by the higher doses, and not affected by the lower doses, of tripelennamine hydrochloride.

Antazoline hydrochloride uniformly diminished locomotor activity. To illustrate this action we calculated the average of the mean locomotor activity per hour, for 4 hours, of each group of 25 rats when used as controls, subtracted this value from all other measurements of hourly mean locomotor activity and expressed the differences as percentages

of the control average. Representative percentage changes in mean locomotor activity after administration of antazoline hydrochloride have been plotted in Figure 1. All depressions of mean locomotor activity by antazoline hydrochloride shown in Figure 1 were significant at the 1 per cent. or less level calculated by the method of Bradford Hill[12], except those after administration of the 2 mg./kg. dose.

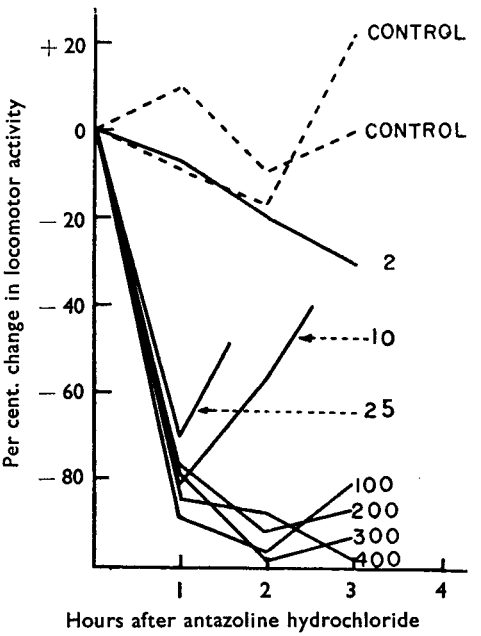

FIG. 1. The effect of antazoline hydrochloride upon the mean locomotor activity of albino rats. The figures indicate the dosage in mg./kg.

DISCUSSION

The data described above indicate that antazoline hydrochloride has, while tripelennamine hydrochloride has not, what could be described categorically as sedative activity in the albino rat. Since sedative activity is one of the most commonly found side-reactions to antihistamine drug therapy in man, an attempt was made to correlate these laboratory findings with reports of sedation in man.

Sedation from use of tripelennamine is the more commonly appreciated side-reaction, as noted by Beckman[13]. Untoward excitation of the central nervous system has been reported by Feinberg and Friedlaender[14], Henderson and Rose[15], Brown[16] and by Churchill and Gammon[17]. Brown[16] emphasised the importance of controlled clinical assessment of side-reactions. He found that many symptoms classified as side-reactions to administration of tripelennamine hydrochloride, could be duplicated by giving placebo tablets. Antazoline hydrochloride has been reported by some to cause no sedation (e.g., Overton[18]) and by others to produce sedative side-reactions (e.g., Britton[19], Waldbott[20] and Dunlop[21]).

SUMMARY

1. Tripelennamine hydrochloride and antazoline hydrochloride were administered orally and subcutaneously, in amounts of from 1 mg./kg. body weight up to lethal doses, to albino rats assembled in Wahmann vertically-revolving drums for the recording of locomotor activity.

2. Tripelennamine hydrochloride had a statistically insignificant effect upon locomotor activity, while antazoline hydrochloride depressed locomotor activity.

The authors wish to acknowledge the assistance of Marion A. Boyd, Elizabeth A. Hineman, J. C. Coates, Jr., and H. D. McEwen, and the receipt of a grant to Queen's University in aid of the out-of-pocket technical expenses of this investigation from the Ciba Company Limited of Montreal through the courtesy of Dr. Fred Wrigley.

REFERENCES

1. Baird and Boyd, *J. Pharm. Pharmacol.*, 1954, **6**, 38.
2. Chen and Portman, *Arch. Neurol. Psychiat. Chicago*, 1952, **68**, 498.
3. Swinyard, Jolley and Goodman, *Proc. Soc. exp. Biol. N.Y.*, 1950, **75**, 239.
4. Kutscher and Chilton, *Amer. J. med. Sci.*, 1952, **223**, 239.
5. Boyd and Boyd, *Canad. J. Med. Sci.*, 1953, **31**, 320.
6. Boyd, Boyd and Cassell, *Canadian med. Ass. J.*, 1954, in press.
7. Griffith and Farris, *The Rat in Laboratory Investigation*, Lippincott, Montreal, 1942.
8. Shirley, *J. comp. Psychol.*, 1928, **8**, 23.
9. Skinner, *J. gen. Psychol.*, 1933, **9**, 3.
10. Mayer, Hays, Brousseau, Mathieson, Rennick and Yonkman, *J. Lab. clin. Med.*, 1946, **31**, 749.
11. Schindler, *Schweiz. med. Wschr.*, 1946, **76**, 300.
12. Bradford Hill, *Principles of Medical Statistics*, 5th edition, The Lancet Limited, London, 1950.
13. Beckman, *Pharmacology in Clinical Practice*, Saunders, Philadelphia, 1952.
14. Feinberg and Friedlaender, *Amer. J. med. Sci.*, 1947, **213**, 58.
15. Henderson and Rose, *Canadian med. Ass. J.*, 1947, **57**, 136.
16. Brown, *Proc. Soc. exp. Biol. N.Y.*, 1948, **67**, 373.
17. Churchill and Gammon, *J. Amer. med. Ass.*, 1949, **141**, 18.
18. Overton, *Brit. med. J.*, 1948, **1**, 874.
19. Britton, *Lancet*, 1947, **253**, 870.
20. Waldbott, *J. Amer. med. Ass.*, 1947, **135**, 207.
21. Dunlop, *J. Pharm. Pharmacol.*, 1949, **1**, 1.