Chlorpromazine Hyperthermia in Young Albino Mice

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The intraperitoneal administration of chlorpromazine hydrochloride to albino mice, ranging in age from 10 to 38 days, caused hyperthermia in the younger and hypothermia in the older animals. No significant difference due to sex was observed in the effect of the drug at different ages.

THE BODY temperature of the homoiothermic vertebrate, contrary to the poikilothermic animal, is controlled within narrow limits by hypothalamic coordinating centers which maintain a delicate balance between heat production and dissipation, and function independently of environmental thermal changes (1). In 1951, during the preliminary pharmacologic investigations of the phenothiazine tranquilizers, it was observed by Courvoisier and her co-workers (2) that chlorpromazine could temporarily transform an homoiotherm into a poikilotherm, an effect later denied by Decourt, *et al.* (3). Later that year, despite this controversy, Laborit and Huguenard (4) introduced chlorpromazine into clinical medicine as a preoperative drug in conjunction with promethazine and meperidine (the lytic cocktail), a combination that caused a fall in body temperature with the attainment of a state of "artificial hibernation," presumably conducive to the prevention of postoperative shock. The hypothermic action of chlorpromazine in a wide variety of mature animals, including mice (1, 5–7), is now well established, and many factors have been found which affect this response (6, 8–13), yet a paucity of information exists in the literature with regard to the effect of this agent on the normal body temperature of immature animals. Therefore, it was the purpose of this study to observe the effects of chlorpromazine when administered to young mice of various ages.

EXPERIMENTAL

Albino mice (1321) (Huntingdon Farms, Inc., HTF strain) were divided into nine groups, each containing from 116 to 238 animals, according to age as follows: 10, 15, 20, 25, 27, 30, 31, 35, and 38 days old. The variation in age of mice within a group did not vary more than 15 hours. With the exception of the youngest age groups (10 and 15 days), each group was equally divided as to sex. Food was withdrawn 15 minutes and water 1 hour before experimentation to provide for nutritional constancy. Temperature recordings, to the nearest 0.1°, were determined orally immediately prior to and 30 minutes after each injection with a model 43 Tele-Thermometer equipped with a No. 402 probe.[1] During testing, each animal was confined in a 100-ml. glass beaker with a screen top, and kept at a constant environmental temperature of 38° 15 minutes before injection and throughout the 30-minute observation period. Freshly prepared aqueous solutions of chlorpromazine hydrochloride[2] were administered at a dosage level of 1 mg./Kg., a dose known to produce hypothermia in mature mice (5, 7), to one-half of a group (equally divided as to sex), while the remaining mice received distilled water and served as controls. All injections were given intraperitoneally at a fixed volume of 0.1 ml.

RESULTS AND DISCUSSION

The effect of chlorpromazine hydrochloride, administered intraperitoneally at a dosage level of 1 mg./Kg., on the body temperature of young albino mice was shown to be influenced by age as recorded in Table I. From the data obtained from 1321 animals, the differences between "before" and "after" temperatures and means for each group were calculated. The significance of differences between means was estimated by use of the *t* test and results are shown in Table II. Only probability levels of 5% or below are indicated. It can be seen that the differences between drug and control groups are significant at extremes of age only, and that there is no evidence that the differences at ages of 20 through 30 days could not have occurred by chance.

Differences between male and female groups at every age are small, and it could be similarly shown that they do not reach levels of statistical significance.

Even if the male and female groups are combined for ages 20 through 31 days, as in Table III, only the 30 and 31-day-old groups reach the 5% level of probability; thus, there is no evidence of either hyperthermia or hypothermia at the ages of 20, 25, or 27 days.

In order to test the significance of the drug × age interaction, the male and female groups were combined and tables of random numbers were used to discard three cases from the 25-day-control group, two from the 27-day-control group, two from the 30-day-drug group, and two from the 38-day-control group, leaving numbers in groups as shown in Table IV. An analysis of variance was then performed as shown in Table V.

Received April 28, 1961, from the School of Pharmacy, Temple University, Philadelphia 40, Pa.

Accepted for publication November 6, 1961.

Abstracted from a thesis presented to the Graduate School of Temple University, School of Pharmacy, by Walter J. Bagdon in partial fulfillment of the requirements for the degree of Master of Science.

Presented to the Scientific Section, A.PH.A., Chicago meeting, April 1961.

The authors are indebted to Dr. A. A. Sugerman for the statistical analysis and to Dr. Neil Chilton for his technical advice.

[1] Yellow Springs Instrument Co., Yellow Springs, Ohio.

[2] Marketed as Thorazine by Smith Kline & French Laboratories, Philadelphia 1, Pa.

TABLE I.—EFFECT OF CHLORPROMAZINE HYDROCHLORIDE ON THE BODY TEMPERATURE OF YOUNG ALBINO MICE[a]

	No. of Mice	Sex	Wt., Gm.	Temperature, °C. Initial	Final	Change	Chlorpromazine Change
10-Day-old							
Drug	106	..	4.73	35.94	37.42	+1.48	+0.91
Control	106	..	4.79	35.92	36.49	+0.57	
15-Day-old							
Drug	60	..	7.27	37.12	37.54	+0.42	+0.74
Control	60	..	7.23	37.27	36.95	−0.32	
20-Day-old							
Drug	28	M	9.27	37.19	37.24	+0.05	+0.14
Control	30	M	9.97	37.08	36.99	−0.09	
Drug	30	F	9.24	37.63	37.66	+0.03	+0.01
Control	28	F	9.78	36.81	36.83	+0.02	
25-Day-old							
Drug	35	M	12.32	37.67	37.51	−0.16	−0.12
Control	34	M	12.39	37.50	37.46	−0.04	
Drug	33	F	12.47	37.69	37.57	−0.12	0.00
Control	37	F	12.17	37.53	37.41	−0.12	
27-Day-old							
Drug	29	M	12.78	37.72	37.64	−0.08	−0.07
Control	30	M	12.35	37.43	37.42	−0.01	
Drug	29	F	12.10	37.71	37.65	−0.06	0.00
Control	30	F	12.13	37.50	37.44	−0.06	
30-Day-old							
Drug	61	M	16.48	37.38	37.16	−0.22	−0.22
Control	58	M	15.57	37.46	37.46	0.00	
Drug	59	F	15.48	37.40	37.19	−0.21	−0.13
Control	60	F	15.45	37.75	37.67	−0.08	
31-Day-old							
Drug	30	M	17.73	36.93	36.57	−0.36	−0.32
Control	31	M	17.53	36.99	36.95	−0.04	
Drug	29	F	17.40	37.16	36.89	−0.27	−0.25
Control	28	F	17.35	37.18	37.16	−0.02	
35-Day-old							
Drug	29	M	20.44	37.01	36.48	−0.53	−0.50
Control	29	M	20.06	36.46	36.43	−0.03	
Drug	30	F	18.54	36.87	36.49	−0.38	−0.37
Control	30	F	18.48	36.47	36.46	−0.01	
38-Day-old							
Drug	34	M	19.81	36.74	36.10	−0.64	−0.62
Control	34	M	20.22	36.78	36.76	−0.02	
Drug	36	F	18.80	36.48	36.06	−0.42	−0.40
Control	38	F	18.54	36.67	36.65	−0.02	

[a] Drug administered intraperitoneally, 1 mg./Kg.

TABLE II.—SIGNIFICANCE OF DIFFERENCES BETWEEN MEANS FOR EACH GROUP, ESTIMATED BY THE *t* TEST

Age, day	Sex	Drug *N*	Drug Mean	Control *N*	Control Mean	Diff.	*t*	*P*
10	..	106	1.485	106	0.574	0.911	6.55	0.001
15	..	60	0.418	60	−0.318	0.736	5.14	0.001
20	M	28	0.054	30	−0.090	0.144	0.88	[a]
20	F	30	0.033	28	0.021	0.012	0.06	[a]
25	M	35	−0.154	34	−0.035	−0.119	0.82	[a]
25	F	33	−0.118	37	−0.119	0.001	0.001	[a]
27	M	29	−0.079	30	−0.003	−0.076	0.43	[a]
27	F	29	−0.062	30	−0.060	−0.002	0.01	[a]
30	M	61	−0.220	58	−0.000	−0.220	1.86	[a]
30	F	59	−0.215	60	−0.078	−0.137	1.09	[a]
31	M	30	−0.357	31	−0.039	−0.318	2.33	0.05
31	F	29	−0.269	28	−0.011	−0.258	1.78	[a]
35	M	29	−0.531	29	−0.021	−0.510	2.58	0.02
35	F	30	−0.373	30	−0.013	−0.360	2.11	0.05
38	M	34	−0.638	34	−0.024	−0.614	4.05	0.001
38	F	36	−0.425	38	−0.021	−0.404	3.07	0.01

[a] No significance.

It is seen (Table V) that the drug × age interaction is significant; i.e., the effect of the drug is different as age increases, and by inspecting the table of differences (Table II), it is seen that this effect is to increase temperature in the lower age groups and to reduce it in the higher age groups.

The significant main effect of age shown in Table V is of much less interest; by inspection of Table II

TABLE III.—SIGNIFICANCE OF DIFFERENCES BETWEEN MEANS FOR COMBINED GROUPS, ESTIMATED BY THE *t* TEST

Age, day	Drug		Control		Diff.	*t*	*P*
	N	Mean	*N*	Mean			
20	58	0.043	58	−0.036	0.079	0.65	[a]
25	68	−0.137	71	−0.079	−0.058	0.57	[a]
27	58	−0.071	60	−0.032	−0.039	0.27	[a]
30	120	−0.218	118	−0.039	−0.179	2.07	0.05
31	59	−0.314	59	−0.027	−0.287	2.89	0.01

[a] No significance.

TABLE IV.—MODIFIED CONTROL GROUPS

Age, day	Drug	Control
10	106	106
15	60	60
20	58	58
25	68	68
27	58	58
30	118	118
31	59	59
35	59	59
38	70	70
Total N = 1312		

we can interpret this as reflecting the increasing hypothermia with age shown in the control groups as well as in the chlorpromazine groups.

To test for the presence of a significant drug × age × sex interaction, the two lowest age groups, undifferentiated as to sex, were discarded, and, as before, cases were discarded from the remaining groups using a table of random numbers, leaving numbers in groups as shown in Table VI. An analysis of variance was then performed which showed no significant age × sex × drug interaction, no significant sex × drug or sex × age interaction, or main effect of sex (*F* values, respectively, 0.29, 1.41, 0.17, and 0.24). Thus, there is no evidence that the change in effect of drug with age is different as between males and females.

SUMMARY

1. The data show that the effect of chlorpromazine on body temperature is influenced by age, the drug causing significant hyperthermia in 10 and 15-day-old mice and hypothermia in 35 and 38-day-old mice.

2. There is no significant evidence of a difference in the effect of chlorpromazine at various ages due to sex.

TABLE V.—ANALYSIS OF VARIANCE FOR TABLE IV DATA

Source of Variation	*df*	*MS*	*F*	*P*
Drug	1	1.16	2.19	not signif.
Age	8	30.72	57.96	0.001
Drug × age	8	10.41	19.64	0.001
Within cells	1294	0.53		
Total	1311			

TABLE VI.—GROUPS USED TO TEST FOR SIGNIFICANT DRUG × AGE × SEX INTERACTION

Age, day	Drug		Control	
	Male	Female	Male	Female
20	28	28	28	28
25	33	33	33	33
27	29	29	29	29
30	58	58	58	58
31	28	28	28	28
35	29	29	29	29
38	34	34	34	34
Total N = 956				

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