นิพนธ์ต้นฉบับ

Does chlorpheniramine maleate has an effect on development of mouse cortical barrels?

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A study of the effect of chlorpheniramine maleate on the development of cortical barrels was undertaken in mice. The drug was given at 20, 30 and 40 mg/kg body weight to three groups of mice at 10 days of pregnancy. The injection was repeated every day until 20 days of pregnancy. Four observations were performed on the mouselings: (1) study of the teratogenic effect of chlorpheniramine; (2) study of the development of the barrels by the Nissl-method; (3) study of the size of the barrel area and the number of neurons at different postnatal ages; (4) study of the thickness of the cerebral cortex.

Findings by comparison of chlorpheniramine treated with control mice were: (1) congenital malformation and resorption of the fetuses were induced by the drug; (2) no significant change in the development of the barrels; (3) the barrel field area and the number of neurons were not affected by the drug; (4) there was no significant difference in the thickness of the cerebral cortex at different ages.

These results indicate only teratogenic effect of chlorpheniramine in mice. The surviving animals revealed normal development of the barrels.

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ราตรี สุดทรวง, นฤมล กิจทวีปวัฒนา, ภาวิช ทองโรจน์. คลอเฟนิรามีนมาลีเอตมีผลต่อการเจริญของบาร์เรลของหนูเมาซ์หรือไม่? จุฬาลงกรณ์เวชสาร 2530 มิถุนายน ; 31 (7) : 453-464

การเกิดความพิการแต่กำเนิดในทารกที่มารดาได้รับยาต้านฮีสตามีนในระหว่างตั้งครรภ์ก่อให้เกิดความปลอดภัยในการใช้ยา คลอเฟนิรามีนซึ่งเป็นยาต้านฮีสตามีนที่ใช้กันมากก็มีรายงานถึงความผิดปกติแต่กำเนิด และพบความผิดปกติของสมองจากการได้รับคลอเฟนิรามีนในขนาดสูง ๆ ในหนูขาว รายงานนี้ คณะผู้วิจัยได้ศึกษาถึงผลของคลอเฟนิรามีนที่มีต่อการเจริญเติบโตของร่างกาย และการเจริญเติบโต ขนาด และจำนวนเซลล์ประสาทบริเวณบาร์เรลของ cerebral cortex และความหนาของ cortex ในหนูไมซ์ โดยฉีดคลอเฟนิรามีนในขนาด 20, 30 และ 40 กรัมต่อน้ำหนักตัว 1 กิโลกรัม ในหนูที่ตั้งครรภ์ได้ 10 วัน และฉีดติดต่อกันทุกวันจนครบ 10 วัน พบว่าน้ำหนักตัวของแม่หนูก่อนคลอดและหลังคลอดลดลงอย่างมีนัยสำคัญทางสถิติ น้ำหนักตัวและน้ำหนักสมองของลูกหนูอายุ 1 - 7 วัน ลดลงอย่างมีนัยสำคัญ อัตราตายของลูกหนูและการมีลูกหนูตายฝังตัวในมดลูก และอุบัติเหตุการเกิดเลือดออกใต้ผิวหนังเพิ่มขึ้นอย่างมีนัยสำคัญ ความผิดปกติแต่กำเนิดในกลุ่มที่ได้รับยาที่พบคือ ลูกหนูไม่มีตาทั้ง 2 ข้าง มีลำไส้ยื่นออกจากผนังหน้าท้อง เท้าแป และมีปากแหว่ง สำหรับการเจริญเติบโตของบาร์เรล ขนาด จำนวนเซลล์ประสาท และความหนาของ cortex ในลูกหนูอายุ 1 - 60 วันนั้น ไม่มีความแตกต่างกันระหว่างกลุ่มควบคุมและกลุ่มที่ได้รับยา

Chlorpheniramine, the p-chloro analogue of brompheniramine is a potent antihistamine which has been available for medical use since 1951. This compound has proved to be relatively nontoxic in the usual dose, at though it does frequently give rise to bothersome side effects. Siriwongse and his colleagues[1] studied teratogenic effect of chlorpheniramine in rats and found that congenital malformation and resorption of the fetuses were induced by the drug. Although dosage in man is much lesser than those given to rats, great care must be exercised in sensitive women when taking this drug, particularly during the first three months of pregnancy. Other antihistamines in the same group (H_1 blocker), such as meclizine, cyclizine and chlorcyclizine, also have been demonstrated to have teratogenic effect in laboratory animals, and their use is contraindicated in pregnant women. [2, 3]

For a number of years, various anatomical investigations have been done on the unusual structure of layer IV of somatosensory system of the mouse, which is characterized by discrete cellular aggregates called "barrels" [4, 5, 6, 7] Each barrel is composed of a cylinder of cells that surrounds a less cellular, central hollow. The nearly acellular area surrounding each barrel, separating adjacent barrels, is called the septum.[5] The cytoarchitectonic region, which contains the barrels, is most easily recognized in tangential sections. A particularly striking and constant portion of the barrel field is the posteromedial barrel subfield (PMBSF), in which the barrels are characterized by their greater size, elliptical shape, organization into five distinct rows, and constant number. Each barrel in the PMBSF is related in a one-to-one fashion to a single vibrissa on the contralateral face.[8, 9] The first signs of organization of the barrel formation within the mouse barrel field are detectable in Nissl preparations between days 4 and 5 (day 1 being the day of birth) by day 6 the whole array appears completely.[10]

We had reported the effect of protein malnutrition on the development of mouse cortical barrels[11] and found that there were a two-day delay in the development of the barrels, a two-day lengthening of the period of vulnerability of barrel field neurons to neonatal vibrissal damage, and that the barrel field area and the relative number of neurons were reduced, with the percentage of reduction decreasing with age. We also studied the effects of monosodium glutamate[12] and lead poisoning[13] on the development of mouse cortical barrel and reported the reductions of the barrel field area and the relative number of neurons, although the mature cytoarchitectonic cortical barrel pattern were normal. As the same techniques had already been developed in our laboratory, we would like to know whether chlorpheniramine meleate also has an effect on the development of mouse cortical barrels as it was demonstrated to have teratogenic effect.therefore in the present study we have investigated the effect of chlorpheniramine meteate on the development of mouse cortical barrels and its teratogenicity.

Meterials and methods

Breeding of mice and administration of the drug

Swiss albino mice, 8 - 12 weeks of age, were given ad libitum access to water and diet (pellets) for 1 - 2 weeks prior to conception. The animals were mated by caging one male with two females. Time of conception was determined by the appearance of vaginal plugs and/or vaginal smear. The pregnant mice were then individually caged. Chlorpheniramine maleate was given intramuscularly at 20, 30 and 40 mg/kg body weight daily to three groups of mice from the 10^{th} to 20^{th} day of pregnancy (n = 37, 40 and 47 respectively). Since Rice[14] found that neurons of layers IV and V of the somatosensory cortex are formed on gestational day 10 - 13, and the genesis of layer IV is on gestational day 14. The onset of maturation of layer IV as defined by the initial appearance of barrel is on the postnatal day (PND) 4.[10]

The cages were examined daily for the pressence of young, and the day of birth was counted as the first postnatal day (PND 1). At various ages following birth, mouselings were weighed and perfused with neutral formalin. After perfusion, the brains were removed and weighed immediately for all animals studied.

Study of the development of barrels

Control mice (from mothers injected with distilled water, n = 52) and three groups of mice (from mothers injected with chlorpheniramine maleate at three different doses (n = 56, 58 and 55 respectively), of accurately timed ages (1-12 days), were perfused with neutral formalin. Frozen sections through the barrel field tangential to the pia were stained by the Nissl method.

Study of the number of neurons and size of barrels

Control and chlorpheniramine treated offspring mice aged 9, 12, 15, 21 and 60 days of both sexes were used. The animals were perfused with neutral formalin. Serial sections 50 microns thick were cut in a plane parallel to the pia overlying the barrel field. The entire PMBSF in each hemisphere were reconstructed, and barrel C-1 was located. All neurons within barrel C-1 boundaries were traced by using a

large central nucleolus and visible cytoplasm as the main criteria for identification. Astrocytes, oligodendrocytes, capillary endothelial cells and cells which appeared to be neurons but lacked an identifiable nucleolus were not traced. Cross-sectional areas of both the entire PMBSF and barrel c-1 were determined.

Study of the thickness of cerebral cortex

Control and drug injected mouselings aged 9, 12, 15, 21 and 60 days were used in this study. Coronal section through the barrel field were stained by Nissl method. The thickness of the cerebral cortex in each specimen was measured.

Result

Effect of chlorpheniramine on pregnant mice and its teratogenicity.

Table 1 shows effects of chlorpheniramine on pregnant mice. As the dose of 40 mg/kg body weight 10 % of the pregnant mice died before delivery. Body weight gain was less in chlorpheniramine injected mice than in control mice ($p < 0.005$). Percentage of mouselings after delivery dying in chlorpheniramine injected groups doses 20, 30 and 40 mg/kg body weight are 37, 40 and 44 respectively, while in control mice only 3 % of mouselings died.

No abnormal mouselings was found in the control group. A dose of 20 mg/kg body weight produced subcutaneous bleeding in 3.79 % new born mice (table 2). At 30 mg/kg, fetal resorption, subcutaneous bleeding, and eventration (Fig. 1A) were found in 5.42 %, 1.51 % and 0.30 % of the off spring mice respectively. The largest dose (40 mg/kg) induced 5% fetal resorption, 2.19% subcutaneous bleeding, 0.93 % bilateral anophthalmia (Fig. 1B), 0.63 % club foot (Fig. 1C), and 0.31 % cleft lip (Fig. 1D).

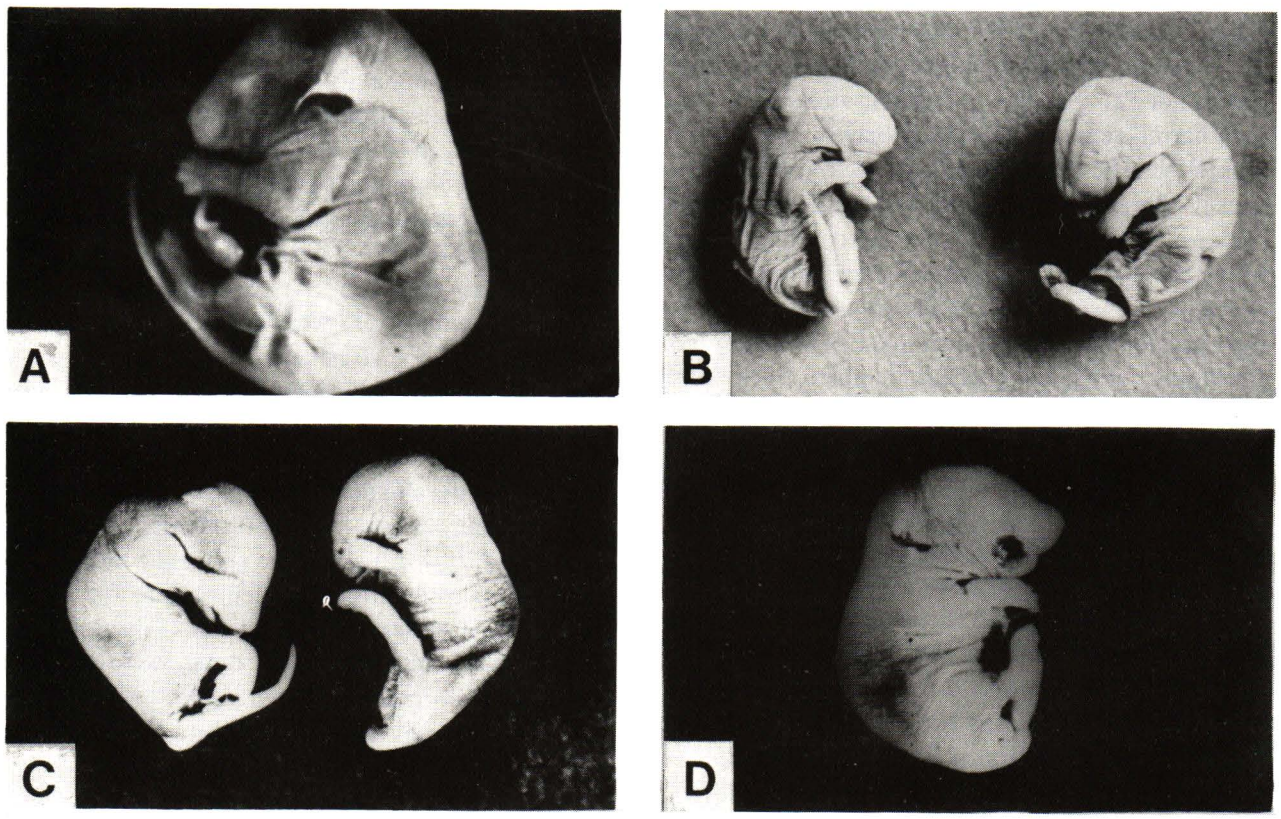

Figure 1 Malformation in mouselings produced by chlorpheniramine maleate injection
A eventration
B bilateral anophthalmia
C club foot
D cleft lip

Table 1 shows the effects of chlorpheniramine on **pregnant mice.**[1]

	Control	Chlorpheniramine Maleate (mg/kg body weight)		
		20	30	40
Total number of pregnant mice	21	37	40	47
Percentage of pregnant mice died before delivery	0	8.11 NS	7.50 NS	10.60 NS
Average total weight gain in pregnant mice (g)	22.15 ± 4.2	18.24 ± 4.4 $p < 0.05$	18.06 ± 4.12 $p < 0.025$	16.53 ± 5.2 $p < 0.005$
Average duration of gestation (days)	20.09 ± 0.76	19.97 ± 0.73 NS	19.89 ± 1.14 NS	19.92 ± 1.13 NS
Average number of mouselings per mother	9.67 ± 2.72	7.76 ± 3.2 NS	8.79 ± 2.23 NS	7.62 ± 2.95 $p < 0.05$
Percentage of mouselings died after delivery	3.45	37.12 $p < 0.005$	40.06 $p < 0.005$	44.69 $p < 0.005$

1 = Values are expressed as mean ± S.D
P = Propability
NS = Not significant

Table 2 Percentage and probability of anomalies in mouselings

Anomalies	Control	chlorpheniramine Maleate (mg/kg body weight)		
		20	30	40
Resorption	-	-	5.42 % $p < 0.005$	5 % $p < 0.005$
Subcutaneous bleeding	- -	3.79 % $p < 0.005$	1.51 % NS	2.19 % $p < 0.05$
Bilateral anophthalmia	-	-	-	0.93 % NS
Club foot	-	-	-	0.63 % NS
Eventration	-	-	0.30 % NS	-
Cleft lip	-	-	-	0.31 % NS

NS = Not significant
P = Probability

Body weights and brain weights of selected age groups of control and chlorpheniramine injected offspring mice are presented in Figures 2A, 2B and table 3. At 1 to 7 days of age, body weights and brain weights at all dosages of chlorpheniramine were significantly less than control group ($p < 0.05$). From 7 to 60 days of age there was little difference in brain and body weights between the control and drug injected groups.

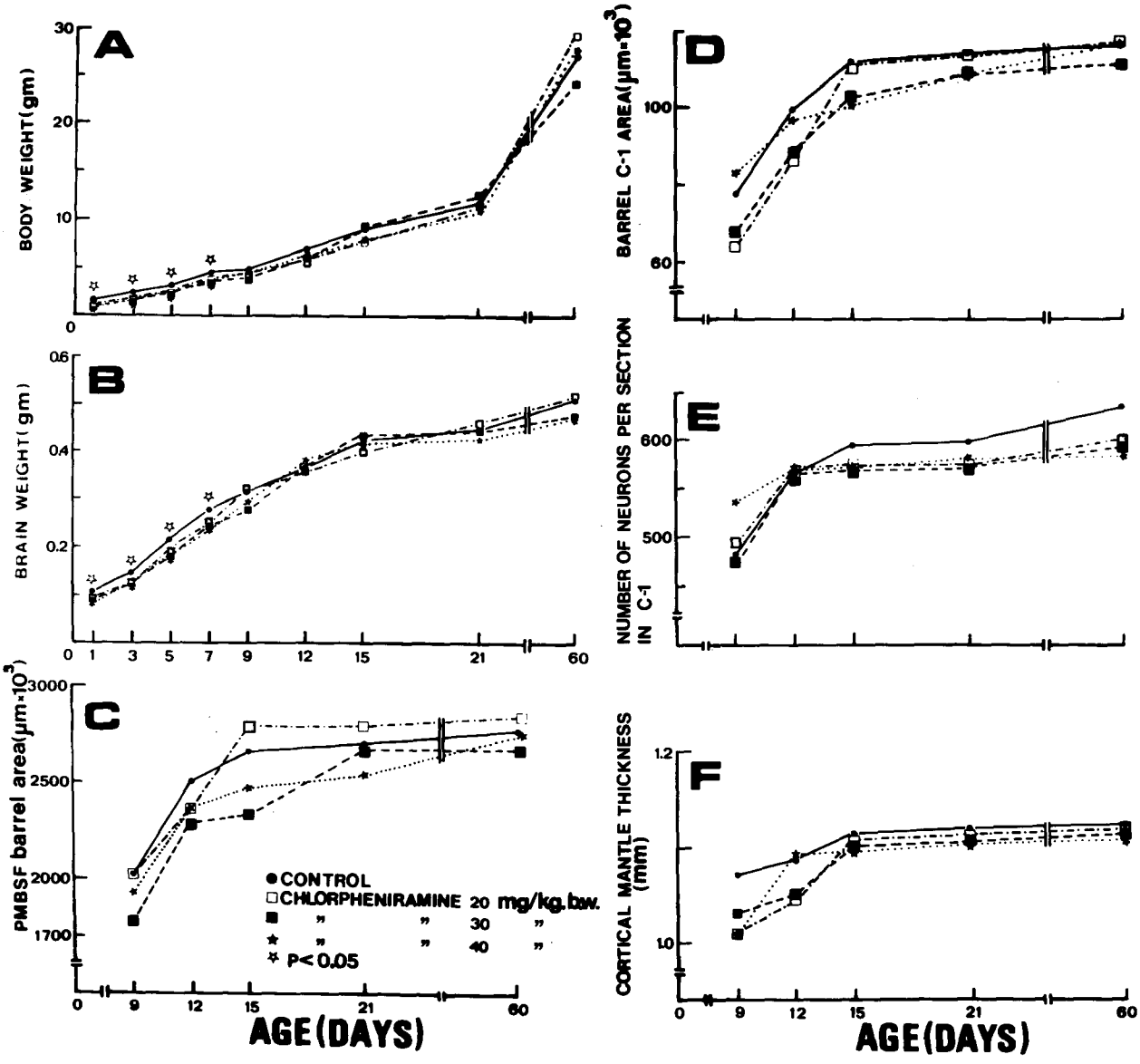

Figure 2 Effect of chlorphenirmine maleate on body weight (A), brain weght (B), PMBSF barrel area (C), barrel C-1 (D). number of neurons (E), and cortical mantle thickness (F) at different ages.

Table 3 Effect of chlorpheniramine maleate on body weight and brain weight in mouselings at different postnatal ages.[1]

PND[2]	control		Chlorpheniramine 20 mg/kg						Chlorpheniramine 30 mg/kg						Chlorpheniramine 40 mg/kg					
	Body weight	Brain weight	mean ± S.D	%	P[3]	mean ± S.D	%	P[3]	mean ± S.D	%	P[3]	mean ± S.D	%	P[3]	mean ± S.D	%	P[3]	mean ± S.D	%	P[3]
1	1.611 ±0.14 (n=9)	0.1057 ±.0069	1.317 ±0.12 (n=9)	-18.23	< 0.001	0.0955 ± 0.029	- 9.65	< 0.025	1.3367 ±0.23 (n=6)	-17.04	< 0.025	0.0933 ±0.011	-11.73	< 0.025	1.1224 ±0.13 (n=8)	-24.03	< 0.001	0.0832 ±0.007	-21.29	< 0.001
5	3.205 ±0.45 (n=5)	0.2187 ±0.01	2.809 ±0.27 (n=9)	-12.36	< 0.05	0.1970 ±0.016	- 9.92	< 0.05	2.7634 ±0.42 (n=12)	-13.78	< 0.05	0.1799 ±0.018	-17.74	< 0.001	2.656 ±0.53 (n=9)	-17.14	< 0.05	0.1834 ±0.019	-16.14	< 0.005
7	4.634 ±0.56 (n=5)	0.2775 ±0.016	4.051 ±0.83 (n=8)	-12.60	< 0.05	0.249 ±0.025	-10.27	< 0.05	3.6989 ±0.59 (n=9)	-20.19	< 0.05	0.243 ±0.26	-12.39	< 0.05	3.792 ±0.51 (n=9)	-18.17	< 0.05	0.2343 ±0.022	-15.57	< 0.05
9	4.996 ±0.49 (n=6)	0.3116 ±0.05	4.537 ±0.73 (n=6)	- 8.59	NS	0.319 ±0.036	+ 2.5	NS	4.0234 ±1.75 (n=7)	-19.47	NS	0.2766 ±0.07	-11.23	NS	4.4065 ±0.59 (n=6)	-11.80	NS	0.2951 ±0.026	- 5.29	NS
12	7.0310 ±1.03 (n=6)	0.362 ±0.019	6.027 ±1.42 (n=5)	-14.28	NS	0.3654 ±0.012	+0.94	NS	6.1018 ±1.12 (n=5)	-13.22	NS	0.367 ±0.015	+1.38	NS	6.377 ±1.35 (n=5)	- 9.3	NS	0.371 ±0.07	+2.49	NS
15	9.1135 ±1.24 (n=6)	0.4234 ±0.037	8.046 ±1.26 (n=8)	-11.71	NS	0.4071 ±0.03	- 3.85	NS	9.491 ±1.25 (n=6)	+4.14	NS	0.434 ±0.038	+2.55	NS	7.904 ±1.196 (n=6)	-13.27	NS	0.419 ±0.03	-1.039	NS
21	11.843 ±0.9 (n=7)	0.444 ±0.0197	11.56 ±1.16 (n=6)	- 2.39	NS	0.453 ±0.28	+2.07	NS	12.99 ±1.55 (n=6)	+9.73	NS	0.44 ±0.02	- 0.86	NS	11.129 ±1.47 (n=6)	- 6.02	NS	0.422 ±0.028	- 5.02	NS
60	27.583 ±2.78 (n=6)	0.5058 ±0.016	29.66 ±2.35 (n=5)	+7.53	NS	0.515 ±0.03	+1.82	NS	24.52 ±5.02 (n=6)	-11.09	NS	0.462 ±0.48	- 8.6	NS	27.917 ±3.74 (n=6)	- 5.88	NS	0.469 ±0.046	- 7.26	NS

1 Value are expressed as mean ± S.D.
2. Postnatal day
3. Probability
NS = not significant

Development of Barrels

Fifty two mice from control group and fifty six, fifty eight and fifty five mice from mothers injected with 20, 30 and 40 mg/kg chlorpheniramine respectively were studied (n = 4-5 daily in each group from PND 1-12). In all groups including the control, the earliest barrels were observed between PND 4 and PND 5. The barrels were in orderly array, but the fields were incomplete until PND 6 (Fig. 3).

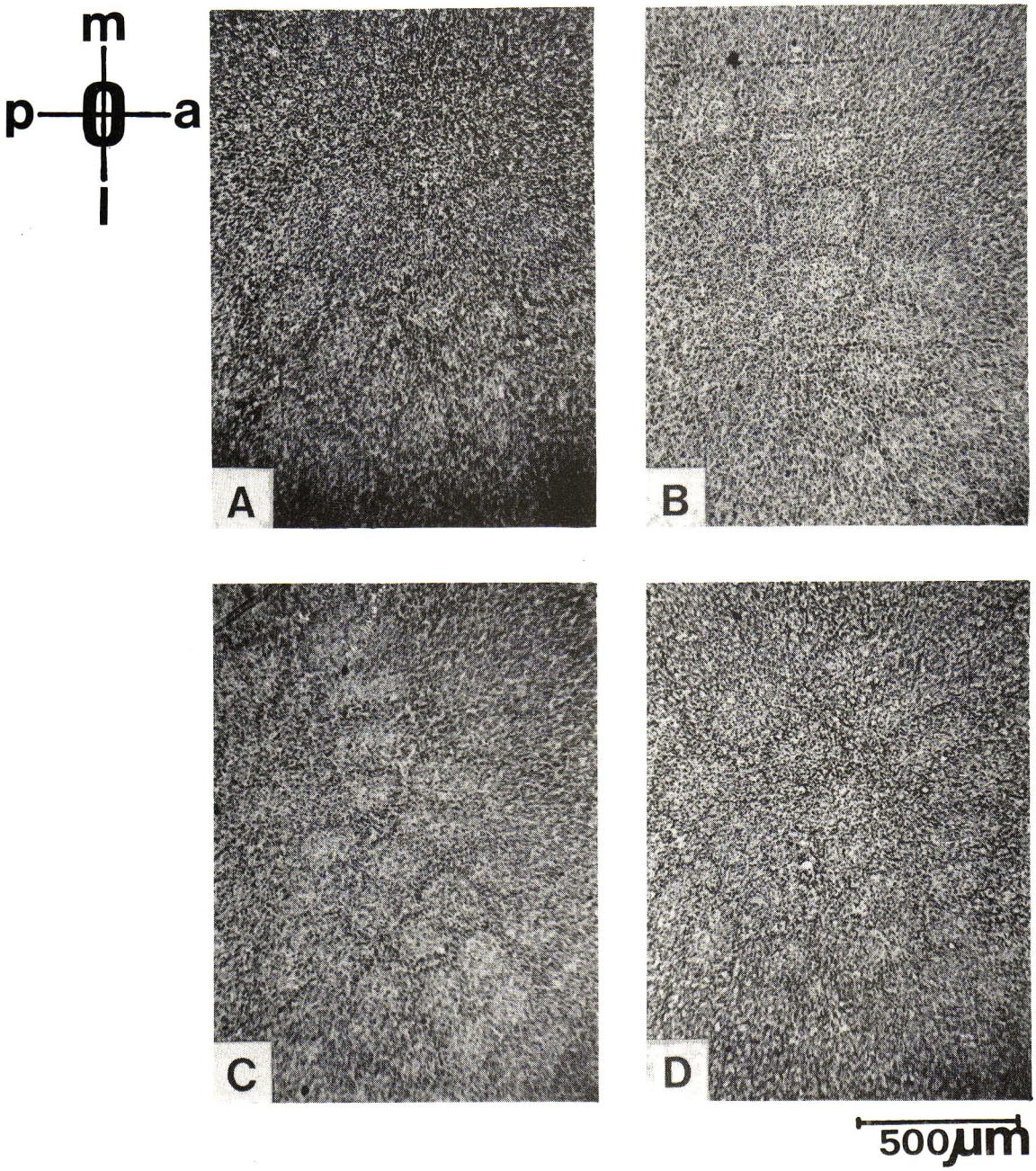

Figure 3 Photomicrographs of section from the right hemisphere of mice from mothers injected with distilled water (A), chlorpheniramine maleate 20 mg/kg body weight (B), 30 mg/kg body weight (C) and 40 mg/kg body weight (D) to show harrels in layer IV of somatosensory cortex in tangential section. Complete barel field were noted on PND 6 in all groups. The whole fields, only partially seen in these single sections, were identified by examination of serial sections. Section are 50 μm thick and stained with cresyl violet. Orientation at the upper left of the figure : m-medial, p-posterior, l-leteral, and a-anterior. All photomicrograph at the same magnification, Bar = 500 μm.

Size of barrel areas and number of neurons at different ages

The areas of the PMBSF and of barrel C-1 were measured, and the ralative numbers of neurons in barrel C-1 were counted in all groups of mice (30 control and 80 drug treated mice) aged 9, 12, 15, 21 and 60 days old. There was no significant difference in barrel areas in both PMBSF and barrel C-1 and number of neurons in all groups of mice compared with the control at the same age (Fig. 2C, 2D, 2E and table 4).

The thickness of the cerebral cortex

Eightly five specimens from all groups of mice aged 9, 12, 15, 21 and 60 days were measured. There was no significant difference in the thickness of the cortex from all groups of mice compared with the control at the same age (Fig. 2F and table 4)

Table 4 Effect of Chlorpheniramine maleate on barrel area, number of neurons and cortical mantle theckness[1]

	No. of animals	PMBSF[2] barrel area ($\mu m^2 \times 10^3$)	Barrel C-1 area ($\mu m^2 \times 10^3$)	Number of neurons per section[3] in C-1	Cortical mantle thickness (mm)
PND 9					
Control	6	2024.72 ± 231.71	77.734 ± 23.29	484.714 ± 77.834	1.6714 ± 0.072 (n=4)
Chlorpheniramine 20 mg/kg	6	2017.42 ± 292.05	63.475 ± 14.096	478.833 ± 84.526	1.0114 ± 0.063 (n=5)
% Changed		-0.36	-18.34	-1.21	-5.6
Probability		NS	NS	NS	NS
Chlorpheniramine 30 mg/kg	7	1769.91 ± 474.59	66.783 ± 24.76	474.571 ± 119.844	1.0286 ± 0.233 (n=4)
% Changed		-12.59	-14.09	-2.09	-3.99
Probability		NS	NS	NS	NS
Chlorpheniramine 40 mg/kg	6	1927.898 ± 94.16	82.86 ± 12.84	536.5 ± 41.27	1.007 ± 0.043 (n=4)
% Changed		-4.93	+6.59	+10.68	-6.002
Probability		NS	NS	NS	NS
PND 12					
Control	6	2506.53 ± 77.43	99.035 ± 8.87	564.83 ± 39.55	1.0857 ± 0.08 (n=6)
Chlorpheniramine 20 mg/kg	5	2298.82 ± 267.61	87.697 ± 10.065	596.60 ± 83.42	1.0429 ± 0.06 (n=4)
% Changed		-8.29	-11.45	+5.62	-3.94
Probability		NS	NS	NS	NS
Chlorpheniramine 30 mg/kg	5	2290.62 ± 224.32	88.42 ± 7.64	576.00 ± 46.92	1.050 ± 0.167 (n=4)
% Changed		-8.61	-10.72	+0.38	-3.29
Probability		NS	NS	NS	NS
Chlorpheniramine 40 mg/kg	5	2357.06 ± 268.91	96.676 ± 19.49	567.60 ± 114.89	1.093 ± 0.59 (n=4)
% Changed		-5.96	-2.38	+0.49	+0.66
Probability		NS	NS	NS	NS
PND 15					
Control	6	2661.177 ± 167.51	112.105 ± 9.77	595.00 ± 59.87	1.1143 ± 0.084 (n=4)
Chlorpheniramine 20 mg/kg	8	2783.163 ± 400.14	111.72 ± 18.34	572.875 ± 91.69	1.107 ± 0.014 (n=4)
% Changed		+4.58	-0.34	-3.72	-3.89
Probability		NS	NS	NS	NS

Table 4 (Continued)

Chlorpheniramine 30 mg/kg	6	2327.075 ± 396.34	102.40 ± 21.23	570.667 ± 81.56	1.100 ± 0.068 (n=4)
% Changed		-12.55	-8.66	-4.86	-1.28
Probability		NS	NS	NS	NS
Chlorpheniramine 40 mg/kg		2469.116 ± 268.018	100.623 ± 9.13	571.50 ± 91.53	1.095 ± 0.067 (n=6)
% Changed		-7.22	-10.24	-3.95	-1.71
Probability		NS	NS	NS	NS
PND 21					
Control	7	2710.087 ± 177.66	114.01 ± 14.65	579.714 ± 35.31	1.120 ± 0.03 (n=5)
Chlorpheniramine 20 mg/kg	6	2790.48 ± 233.37	114.01 ± 14.46	574.33 ± 95.65	1.1143 ± 0.11 (n=4)
% Changed		+2.97	0	-3.912	-0.51
Probability		NS	NS	NS	NS
Chlorpheniramine 30 mg/kg	6	2675.76 ± 198.99	108.578 ± 13.88	574.29 ± 111.397	1.1048 ± 0.12 (n=3)
% Changed		-1.27	-4.76	-3.92	-1.36
Probability		NS	NS	NS	NS
Chlorpheniramine 40 mg/kg	6	2543.94 ± 137.69	108.99 ± 20.01	581.00 ± 122.13	1.103 ± 0.12 (n=5)
% Changed		-6.13	-4.399	-2.796	-8.125
Probability		NS	NS	NS	NS
PND 60					
Control	6	2790.75 ± 216.31	116.32 ± 20.41	682.667 ± 97.496	1.124 ± 0.09 (n=3)
Chlorpheniramine 20 mg/kg	5	2854.15 ± 154.69	116.46 ± 17.78	601.50 ± 45.54	1.121 ± 0.054 (n=4)
% Changed		+2.27	+0.13	-4.32	-0.21
Probability		NS	NS	NS	NS
Chlorpheniramine 30 mg/kg	6	2689.39 ± 215.78	111.96 ± 15.07	593.17 ± 65.11	1.1143 ± 0.10 (n=3)
% Changed		-3.63	-3.74	-5.65	-0.85
Probability		NS	NS	NS	NS
Chlorpheniramine 40 mg/kg	6	2755.685 ± 247.94	116.549 ± 19.98	587.00 ± 43.47	1.109 ± 0.06 (n=5)
% Changed		-1.26	+0.20	-6.63	-1.35
Probability		NS	NS	NS	NS

1. Values are expressed as mean ± S.D.
2. Posteromedial barrel subfield.
3. All sections were cut 50 μm thick.

NS = not significant.

DISCUSSION

It has been shown in this study that chlorpheniramine induced teratogenic effect in mice. If the animals survived, their barrels development were normal. No significant differences were seen in barrel areas, number of neurons and thickness of cerebral cortex between control and drug treated mice at different ages.

Dixon et al[15] has suggested that the teratogenic dose of any chemical would be slightly lower than its LD_{50}. In this study, the doses of chlorpheniramine maleate were lower than its LD_{50}.

Subcutaneous bleeding was common in all groups of mice injected with chlorpheniramine. It has been found that chlorpheniramine induced bone marrow suppression and aplastic anemia[16, 17]. These blood dyscrasias may be the cause of subcutaneous bleeding. The resorption of fetuses was significant at the doses of 30 and 40 mg/kg. Chlorpheniramine may have direct toxic effect on fetuses and result in the resorption in uterus.

The congenital anomalies in mouselings were eventration (Fig. 1A), bilateral anophthalmia (Fig. 1B), club foot (Fig. 1C) and cleft lip (Fig. 1D) all of which were found only in chlorpheniramine treated animals (Table 2). This is in accordance with the work of Siriwonge et al[1] on rats. It can therefore be concluded that a high dose of chlorpheniramine may produce teratogenic effect in mice.

The development of barrels in the control group as well as in the chlorpheniramine injected group was found to be similar to that reported in other studies[9,10] (Fig. 3). Rice[14] has reported that the time of origin of barrel neurons was between the 14^{th} and 16^{th} day after conception. The injection of the drug between 10^{th} and 20^{th} day after conception may have no effect on the development of barrels. Nevertheless total weight gain in pregnant mice and average number of mouselings per mother decreased significantly from the control group (Table 1). Body weight and brain weight of offspring mice aged 1 - 7 days were also significantly decreased ($p < 0.05$). This may be due to the side effects of the drug. It has been reported that this group of antihistamine (H_1 blocker) causes anorexia, nausea, vomiting, epigastric distress, and constipation or diarrhea[18]. The high dosages of the drug may produce some gastrointestinal disturbances in pregnant mice. They may have taken less food than usual and became undernourished. Previous experimental studies showed that undernutrition reduced body weight and brain weight[11, 19, 20]. In this study, undernutrition may not have been severe enough to produce any effect on development of barrels. Vongdokmai[11], breeding protein malnourished mice 6 weeks prior to conception, found a two-day delay in the development of the barrels, and a reduction of barrel field areas and relative number of neurons. Unfortunately, in this study we did not measure the daily food intake. There may be some other mechanisms that could explain the teratogenic effect of the drug which require further studies to support. However, H_1 blooking drugs are excreted rapidly from the body[18]. This may explain why the drug effected the mouselings up to 7 days of age.

The percentage of new born mice dying after delivery as presented in table 1 deserves comment. The significant increase ($p < 0.005$) in death after delivery in the chlorpheniramine treated mice may be due to toxic effects of the drug. The drug may have direct toxicity on the fetuses or may have produced anomalies that inhibit or retard the growth of the fetuses.

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