HYPERSENSITIVE TOXICITY OF 5-n-BUTYL-1-CYCLOHEXYL- 2,4,6-TRIOXOPERHYDROPYRIMIDINE IN THE PREGNANT RAT

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5-n-Butyl-1-cyclohexyl-2,4,6-trioxoperhydropyrimidine (BCP), a new antipyretic antiphlogistic agent, has been reported to differ from aminopyrine and phenylbutazone in lack of central convulsion in mice and rats as well as in mildness of the convulsion caused by the toxic doses in rabbits and dogs (1). Respiratory depression was the usual cause of death following excessive doses of BCP. The oral subchronic toxicity of BCP, aminopyrine and phenylbutazone in rats was reported by Okamoto (2) and Araki (3). According to their results, BCP in the daily doses above 800 mg/kg produced slight degeneration and destruction of the convoluted tubular epithels in the kidney, while phenylbutazone in the lesser doses resulted not only in the similar changes in the kidney, but also in obvious degeneration of the liver cells and the cardiac muscle fibers.

The necessary prerequisite of a clinically available drug should be superiority of the main pharmacological effects and also minority of the side effects. During the toxicological studies of the antiphlogistics, the present author found that the lethal dose of BCP in the pregnant rats was markedly different from that in the non-pregnant ones. Therefore, attempt has been made in the present report whether the lethal response to the compound is conditioned by sex or gestation.

METHODS

Adult male and female rats (4-5 months of age) of Wistar strain were used. The animals were housed in the individual cage at room temperature of $22\pm 2^{\circ}\text{C}$ and at humidity of 40-70%, and were fed a commercial powdered diet (CLEA OA-2, supplied by the Japan CLEA Co.) and water *ad libitum*.

Pregnant rats: Previously unmated two female rats were placed in a cage with a male overnight. Those found to have vaginal plugs were isolated and the day when the females showed the positive smear was regarded as zero day of pregnancy.

Drug administration: BCP, aminopyrine and phenylbutazone were suspended in water at various concentration with carboxymethyl cellulose and administered via stomach tube. The non-pregnant rats were treated with a single dose of 1.0, 1.5 and 2.0 g/kg of BCP and were observed for 7 days. In next series of experiments, BCP in doses of 100-

800 mg/kg/day were orally administered once a day in every morning of 7 successive days. The pregnant rats were treated with BCP (100–400 mg/kg/day), aminopyrine (200 mg/kg/day) and phenylbutazone (100 mg/kg/day) from the 7th to 13th day of gestation. Control animals received carboxymethyl cellulose suspension alone.

In the chronic experiments the rats of both sexes were given the powdered diet supplemented with 50, 100 and 200 mg/kg/day of BCP and phenylbutazone for 48 weeks.

Body weight and daily food intake were measured every morning in the acute and subacute experiments and once a week in the chronic experiments. Attention was paid to the changes of behavioral and physical symptoms caused by the administration of the test drugs.

Teratogenic tests: Control and surviving pregnant rats treated with the test drugs were sacrificed on the 20th day of gestation. The uteri of the sacrificed rats were carefully removed. The number of implantation sites, living and dead fetuses and resorption of the embryos were counted and the abnormalities in the placenta, umbilical cord and amnion were examined. The living fetuses were grossly described and weighed. They were then cleared, and their skeletons stained with alizarin red S by a modification of the Dawson's method (4) and examined for skeletal abnormalities.

Pathological examinations: The non-pregnant rats were sacrificed by instantaneous decapitation at 7 days after the single administration or at 2 days after the termination of 7 successive administration of BCP.

In the chronic experiments, 4–5 animals in each group were killed at the end of 12th, 24th, 36th and 48th week. All tissues were examined macroscopically and the lung, heart, liver, spleen, gastro-intestinal tract, pancreas, kidney, adrenals, thyroid gland, thymus, testis, prostate, uterus and ovary were fixed for microscopic examination. The animals killed by the toxic manifestation of the test drug were also subjected to detailed gross and microscopic studies.

RESULTS

1. Single administration of BCP

The single doses of BCP (1.0, 1.5 and 2.0 g/kg) were orally administered in the non-pregnant rats and the changes in behavior, body weight, food intake and lethality were observed for 7 days. Each group consisted of 9–10 animals. In the male groups, one

TABLE 1. Mortality in the non-pregnant rats following a single oral administration of BCP.

Doses (g/kg)	Sex	Mortality	(%)	No. of dead animals						
				1	2	3	4	5	6	7 (day)
1.0	Male	0/10	(0)							
1.5	"	1/10	(10)	1						
2.0	"	3/9	(33)		1		1	1		
1.0	Female	1/10	(10)	1						
1.5	"	2/10	(20)	1	1					
2.0	"	3/10	(30)	3						

animal died by 1.5 g/kg and three by 2.0 g/kg. In the female groups one, two and three animals were killed within 48 hours, after the treatment of the compound in doses of 1.0, 1.5 and 2.0 g/kg, respectively (Table 1). No significant difference was observed between the mortality of both male and female groups. Increased locomotor activity and rhinencephalically stimulating behavior such as exploratory locomotion and rubbing the face with fore limbs were observed within the first 1 hour after the oral administration at all

FIG. 1. Body weight change in the non-pregnant rats following a single oral administration of BCP.

41 g and 16 g at the 3rd day, respectively (Fig. 1). It recovered to the previous level at the 5th to 6th day. Thus, the single oral LD_{50} of BCP was above 2.0 g/kg in both males and females.

2. Repeated administration of BCP for 7 days

1) Male rats

The daily administration of 800 mg/kg of BCP to 20 male rats resulted in a marked decrease of the food intake, and the mean intake at the 4th day was about 11 g in contrast to 23–25 g in the non-treated control males. However, the food intake recovered gradually despite the continuation of further treatment with the compound. The body weight of the treated animals hardly increased during 7 days of the administration, though that of the control males increased by 32 g during the same period. Several treated rats showed conjunctival bleeding, profuse salivation and marked decrease of voluntary movement, but no animal died throughout the experimental period (Table 2). The toxic symptoms recovered gradually after the termination of the administration.

doses. Thereafter, all the rats turned to the depression of voluntary movements and some of them showed a complete cessation of voluntary movements. The intoxicated animals showed a marked decrease in the daily intake of food and water during 2–4 days, and ptosis, conjunctival bleeding and profuse salivation were present. These symptoms were followed by muscle rigidity accompanied with sensitivity to tactile stimuli. Dead animals showed an extreme emaciation prior to death. The survived animals recovered gradually from the 3rd to 4th day after the administration.

The single administration of BCP decreased markedly the daily food intake and body weight during 3 days at all doses. The mean reduction in body weight of the male and female rats received 2.0 g/kg was

TABLE 2. Mortality in the pregnant and non-pregnant rats following repeated oral administration of BCP for 7 days.

Doses (mg/kg/day)	Sex	Pregnancy	Mortality (%)	No. of dead animals								Body weight change during the drug administration (g)*
				1	2	3	4	5	6	7	8 (day)	
Control	Male		0/10									+ 32
800	⌘		0/19	(0)								+ 2
Control	Female	Non-pregnant	0/10									+17
200	⌘	⌘	0/20	(0)								+27
400	⌘	⌘	2/10	(20)			1	1				−26
800	⌘	⌘	4/ 9	(44)	1				2	1		−25
Control	⌘	Pregnant	0/22									+27
100	⌘	⌘	0/22	(0)								+ 9
200	⌘	⌘	1/22**	(5)								−40
400	⌘	⌘	18/30	(60)	2	4	3	4	3	2		− 9

*: + (increase), - (decrease).

** : One rat died at the 19th day of gestation.

2) Female non-pregnant rats

The daily administration of 200 mg/kg of BCP to 20 non-pregnant female rats did not produce serious toxic effects, though their body weight gain and daily food intake were slightly reduced during administration period. No animal was killed by this dosage.

On the other hand, mortality in non-pregnant females following repeated administration of 400 and 800 mg/kg for 7 days was 20% and 44%, respectively. The food intake and body weight were markedly reduced and the voluntary movement of the animals was progressively depressed. The mean decrease in the body weight was about 25 g at the 7th day, though the body weight gain in the non-treated control females was 17 g during the same period. Five out of 10 rats received 400 mg/kg and 6 out of 9 rats received 800 mg/kg showed almost complete cessation of the voluntary movement from the 4th day. The conjunctival hyperemia or bleeding, salivation and incontinence of urine were observed in these animals. The body weight and food intake of the survived animals were rapidly recovered after the termination of the drug administration.

3) Pregnant rats

The mean increase in the body weight of 22 pregnant rats during 20 days of gestation was 110.7 g, which consisted of increases by 27 g from the 1st to 7th day, by 27 g from the 7th to 14th day and by 56.7 g from the 14th to 20th day. The daily food intake also increased gradually from 14.0 g at the 1st day of gestation to 20.7 g at the 20th day.

The daily administration of 100 mg/kg of BCP from the 7th to 13th day of gestation did not significantly affect total increase in the body weight (107.8 g) during the pregnancy (Table 3), but the body weight gain during the period of the drug administration was 15.0 g and it was less than that in the control pregnant rats. The daily food intake reduced considerably during the first 2 days of the drug administration. However, no other behavioral difference between the treated and non-treated animals was detected.

TABLE 3. Effects of BCP, aminopyrine and phenylbutazone on pregnant dams and fetuses of the rat.

Drugs	Doses per day (mg/kg)	No. of rats	Dead	Pregnant dams			Fetuses			
				Body weight increase (g)	No. of implants	Weight of placenta (mg)	Alived (%)	Resorbed (%)	Dead (%)	Body weight (mg) Male Female
Control		22	0	110.7	12.0	390.6	11.6 (96.6)	0.4 (3.4)	0	3771 3516
BCP	100	22	0	107.8	13.0	368.2	11.8 (90.6)	1.2 (9.4)	0	3775 3567
	200	22	1	91.5	12.6	365.4	11.6 (91.7)	1.0 (8.3)	0	3528 3352
	400	30	18	62.9	13.4	298.9	11.8 (87.6)	1.6 (11.8)	0.1 (0.6)	3068 2794
Aminopyrine	200	10	0	106.7	13.0	353.5	12.8 (98.5)	0.2 (1.5)	0	3642 3453
Phenylbutazone	100	9	0	88.9	12.3	395.9	11.6 (93.7)	0.8 (6.3)	0	3770 3639

Total increase in the body weight during the pregnancy in the rats received the dose of 200 mg/kg for 7 days was 91.5 g which was significantly less than that in the non-treated rats. The body weight decreased by about 40 g during the administration period. However, this reduction was partially compensated by rapid body weight gain after the final treatment of the compound. The daily food intake also decreased to 6 to 10 g during the administration period. One out of 22 rats died at the 19th day of gestation showing an extreme emaciation. Some of the treated rats exhibited the manifestation of similar toxic symptoms as described above, which disappeared gradually after the last treatment of the compound.

The pregnant rats which received daily dose of 400 mg/kg of BCP for 7 days showed the serious toxic symptoms such as cessation of the voluntary movement, marked decrease in the body weight and food intake, diffuse conjunctival bleeding, profuse salivation and incontinence of urine, and 18 out of 30 treated rats were killed. The survived animals, though they exhibited considerably serious toxic effects, recovered gradually after the termination of the administration. The mean increase in body weight of the survived animals received 400 mg/kg was 62.9 g during the total gestation term, which was markedly less than that in the control pregnant animals. The daily food intake reduced to 10–11 g during the administration period, and it did not readily increase after the last treatment.

3. Repeated administration of aminopyrine and phenylbutazone in the pregnant rats

The daily administration of 200 mg/kg of aminopyrine from the 7th to 13th day of gestation caused a slight decrease of the daily food intake and a cessation of body weight gain during the administration period. The body weight increased rapidly associated with recovery

of the food intake after the termination of the administration. Therefore, the total body weight increase during pregnancy was 106.7 g which was almost the same as that in the control pregnant. No other behavioral abnormality was observed.

The similar treatment of 100 mg/kg of phenylbutazone resulted in the body weight gain by 91.8 g during the total gestation term. The suppression of the body weight increase was due to decrease in the daily food intake during and after the administration period. No other toxic symptom was detected.

4. Teratogenicity

Table 3 summarizes number of implantation sites, and living, resorbed and dead fetuses, and weight of living fetuses and placenta in the control pregnant rats and in the pregnant rats treated with BCP (100–400 mg/kg), aminopyrine (200 mg/kg) and phenylbutazone (100 mg/kg). No significant difference was detected between numbers of implantation sites of both non-treated and treated dams. The ratio of living fetuses to the litter reduced slightly by the treatment of BCP, but not by aminopyrine and phenylbutazone. On the contrary, the ratio of resorption of the embryos increased by BCP. The weight of the living fetuses was significantly reduced in the rats received 400 mg/kg of BCP.

No anomaly in the external appearance and viscera occurred in the offsprings of rats treated with BCP at all doses. Table 4 shows the skeletal abnormalities caused by BCP.

TABLE 4. Number and type of skeletal abnormalities in the fetuses resulting from BCP given to the pregnant rat.

Doses per day (mg/kg)	No. of fetuses	Malformations							
		Skull	Limbs	Cervical vertebrae	Thoracic vertebrae	Lumbar vertebrae	Caudal vertebrae	Ribs	Sternebrae (Mislocated)
Control	305	0	0	0	0	0	0	0	4 (1.3)*
100	260	0	0	0	2 (0.8)	0	0	0	17 (6.5)
200	248	0	0	0	5 (2.0)	4 (1.6)	0	0	38 (15.2)

* : Each value in parentheses represents percentage of malformations to the total fetuses.

There was no anomaly in the skull, limbs, cervical and lumbar vertebrae and ribs. In a few cases, the compound produced abnormalities of the thoracic and lumbar vertebrae such as dislocated, split and flattened ossification of the vertebral bodies. The mislocation of sternebrae increased from 1.3% in the control to 6.5% and 15.3% in the offsprings from the rats treated with 100 and 200 mg/kg of BCP, respectively.

5. Chronic oral toxicity of BCP and phenylbutazone for 48 weeks

Table 5 shows the respective body weight changes in the group of male and female rats fed the powdered diet added with 50, 100 and 200 mg/kg/day of BCP and phenylbutazone for 48 weeks. In the males, the oral administration of 50 and 100 mg/kg/day of BCP and phenylbutazone did not modify the body weight increase for 24 weeks. However, the growth rate was depressed by the administration of 200 mg/kg/day of both compounds. In the females, the doses of 100 and 200 mg/kg/day of BCP and phenylbutazone

TABLE 5. Effect of BCP and phenylbutazone on the body weight gain in the male and female rats for 48 weeks.

	Drugs	Doses (mg/kg/day)	Mean of body weight (g)													
			before	4	8	12	16	20	24	28	32	36	40	44	48 (weeks)	
Male	Control		81	184	261	308	310	319	323	333	335	342	398	405	402	
	BCP	50	81	182	250	291	304	325	331	333	327	330	368	378	368	
		100	81	180	254	292	315	335	345	363	351	338	365	375	360	
		200	81	198	248	286	299	292	303	332	348	337	335	334	331	
		Phenyl- butazone	50	81	193	273	312	338	355	362	368	359	357	324	328	319
	100		81	175	241	285	299	323	330	322	311	319	351	357	353	
	200		81	204	247	273	307	300	308	344	366	354	324	339	347	
Female	Control		95	172	203	223	233	236	240	250	244	249	257	264	252	
	BCP	50	95	157	190	233	214	219	226	230	231	237	237	238	227	
		100	95	157	186	199	207	212	212	215	210	211	206	210	203	
		200	95	160	180	186	191	192	196	202	200	199	190	185	195	
		Phenyl- butazone	50	95	163	198	221	230	233	235	238	222	233	253	258	250
	100		95	161	194	212	211	217	219	218	215	217	238	242	235	
	200		95	164	181	193	198	198	199	219	210	211	196	—	—	

No. of animals in each group : 0-12 weeks : 19-20 rats,
 13-24 " : 12-15 rats,
 25-36 " : 6-10 rats,
 37-48 " : 3-5 rats.

suppressed the body weight increase. The inhibitory effects of both compounds on the body weight gain were more marked in females than in males. From the 28th to 48th week, the body weight increase in the group of animals received high doses of BCP and phenylbutazone was almost the same as that in the control group.

The decrease of the daily food intake was also observed in the groups of male and female rats treated with 200 mg/kg/day of BCP and phenylbutazone for 24 weeks. No animal was killed in the BCP-treated group for 24 weeks except one which was administered 100 mg/kg/day of BCP and died at the 16th week exhibiting the symptoms of pneumonia. On the other hand, 2 and 8 animals died in the groups of male and female animals received 200 mg/kg/day of phenylbutazone until the 24th week, respectively. These dead animals showed the submucosal bleeding and the hypertrophy of the adrenal glands and did not exhibit the symptoms of pneumonia.

No hematological abnormality was found by the administration of BCP and phenylbutazone for 48 weeks. The doses of both compounds did not produce the abnormality of protein, glucose and keton body in the urinary examinations. However, the urobilinogen test showed positive in the group of animals treated with higher doses of phenylbutazone.

6. Pathohistological findings

The non-pregnant rats killed by the toxic manifestation in the single dose of 1.0 and 2.0 g/kg of BCP showed macroscopically the following pathological findings such as pulmo-

FIG. 2. Histological changes of the rats treated with single oral dose of 2.0 g/kg of BCP.
A) Adrenals ($\times 60$), B) Spleen ($\times 60$).

nary and adrenal bleeding, congestion in the right atrium, fullness in the stomach with gas and fluids and subperitoneal bleeding. Histologically, the erythrocytes increased in the alveoles of the lung, kidney, adrenals and other tissues. Especially, the marked bleeding was observed in the fascicular and reticular zones of the adrenals as shown in Fig. 2-A. The liver showed a slight but diffuse edema and turbidity of the acinal cells. The lymphatic structure of spleen showed some atrophic picture but the red pulp was filled with large amounts of the blood cells (Fig. 2-B). The autopsy and histological studies of the survived rats treated with the single doses of BCP demonstrated no pathological signs except the liver which showed some turbidity of the acinal cells.

The macroscopic findings of the tissues in the non-pregnant rats killed by the repeated administration of 400 and 800 mg/kg of BCP for 7 days were almost the same as those in the animals killed by the single doses. However, the histological pictures of the former animals were slightly different from those of the latter. The spleen showed not only atrophic change of the lymphatic follicles but also reduction of the blood cells in the red pulp. In the adrenals, proliferation of the inner structure of the cortex with well-stained cells was observed. The tubular cells of the proximal convolution in the kidney was less staining with desquamated epithels in the canal. However, the survived animals treated with repeated administration of BCP did not show any pathological findings.

In the dead pregnant rats caused by the toxic manifestation of BCP, weight of the adrenals and lung increased significantly and that of the kidney and heart increased

slightly. On the other hand, the liver and spleen showed significant decrease in weight. Histological pictures of the lung of the dead animals showed the diffuse bleeding in the alveoles and congestion in the capillaries. Interstitial capillaries of the heart were also filled with the erythrocytes. In some of the hearts the capillary hemorrhage was localized in the subendocardial space. The hepatic cells in the central and middle parts of acinus were less staining and edematous, though the acinal structure was relatively distinctive. The marked atrophy of the lymphatic follicles was observed in the spleen. Though the blood cells in the red pulp decreased in number, considerably many phagocytes and deposition of the blood pigment were always found. The glomerular epithals of the kidney were less staining and showed fibrous and hyalinous degeneration. The tubular epithels especially in the proximal portion were also less staining and showed destruction of the protoplasmic structure and pycnosis of the nucleus, so that the tubular structures were made less distinctive. Marked congestion in the capillaries was observed at the inner part of the renal cortex. Slight edematous cells were intermingled with diffuse hemorrhage in the fascicular and reticular zones of the adrenals. The glomerular zone was somewhat narrow. The pancreas, gastro-intestinal tract, uterus and ovarium presented no pathological pictures except the congestion in the capillaries. The survived pregnant rats treated with BCP showed almost the similar pathological changes as those

FIG. 3. Histological changes of the rats treated with oral dose of 200 mg/kg/day of BCP for 48 weeks.

A) Adrenals ($\times 60$), B) Thymus ($\times 60$).

of the dead animals. However, the parenchymatous bleeding and the congestion were less in the survived rats than in the dead ones.

In the chronic toxicological studies, the oral administration of BCP and phenylbutazone for 12 weeks produced the proliferation of the fascicular and reticular zones of adrenals. The congestion and hemorrhage in these zones were found in the groups of animals received higher doses of both compounds. On the other hand, the continued administration of BCP and phenylbutazone for 36 to 48 weeks resulted in the atrophy of cells in the inner layers of adrenals (Fig. 3-A). The atrophy of lymphatic systems in the thymus and spleen was observed by higher doses of both compounds at the 12th week (Fig. 3-B). These atrophic changes were also found in the group of animals received 50 and 100 mg/kg/day of BCP and phenylbutazone for 24 weeks and more. Furthermore, the administration of both compounds over 24 weeks caused the proliferation of reticulo-endothelium and the congestion of red pulp in the spleen.

Higher doses of BCP and phenylbutazone produced the decrease of number of cells in the anterior lobe of hypophysis. The follicular epithelia of the thyroid gland showed polymorphism and the follicular colloid was stained lightly. The follicular epithelia of thyroid gland was destructed partly and the number of sperma cells in the testis was reduced by the doses of both compounds.

These pathological changes in the adrenals, thymus, spleen, hypophysis, thyroid gland and testis were more marked in phenylbutazone-treated group than in BCP-treated group and also more severe in the female animals than in the male ones. Furthermore, the proliferation of connective tissues in the intratubular space of kidney was observed in the groups of male rats treated with BCP and phenylbutazone for 24 weeks and more.

DISCUSSION

BCP, a new antipyretic antiphlogistic derivative of pyrimidine, reported to be less toxic to the experimental animals than aminopyrine and phenylbutazone (1). The sub-chronic toxicity study (2, 3) of BCP in the rats proved only a minor pathological damage on the renal tubules in the higher doses. The present experiments also confirmed that the caute oral LD_{50} of BCP in the rats was above 2.0 g/kg. Some of the animals received 1.5 and 2.0 g/kg exhibited the toxic symptoms such as depression of voluntary movement, marked decrease in the daily food intake and conjunctival bleeding. A few animals were killed showing an extreme emaciation. The pathological examinations of the killed animals indicated that the cause of death presumably might be diffuse bleeding in the adrenal cortex. The evidence for the role of aminopyrine and phenylbutazone in the production of clinical leucopenias was repoted by Kracke (4), Etess *et al.* (5) and Leonard (6). It was demonstrated that the gastric ulcer with massive hemorrhage occurred in a patient treated with phenylbutazone (7). Further, damage of the kidney was side effect of phenylbutazone. The present experiments suggested that death caused by the single administration of BCP was likely due to decompensation in function of the adrenal cortex. In this respect, it is assumed that the above-described side effects of aminopyrine

and phenylbutazone are related partly with the adrenal decompensation.

The repeated oral administration of 200–800 mg/kg of BCP for 7 days proved that the female rats showed more sensitive toxicity than the male ones. None of the male rats was killed by the daily dose of 800 mg/kg, while 4 out of 9 females died by the same dose. The histological pictures of the adrenal cortex of these dead animals showed not only diffuse bleeding but also feature of hyperfunction such as proliferation of the cells in the fascicular and reticular zones. Further, successive treatment of BCP produced considerably marked atrophy of the lymphatic follicles in the spleen and diffuse hemorrhage in the various tissues. It was assumed from these findings that the ultimate feature might be abrupt decompensation of the adrenal function. This problem demands further experiments.

The oral repeated administration of BCP and phenylbutazone for 48 weeks confirmed more sensitive chronic toxicity of both compounds in the female rats than in the male ones. Further, the toxicity of phenylbutazone was more marked than that of BCP in both male and female animals. In the chronic experiments, the tissues which showed the pathological pictures were almost the same as those in the animals received the repeated administration of both compounds for 7 days. The oral administration for 12 weeks resulted in the proliferation and bleeding of the cells in the fascicular and reticular zone of adrenals. However, the continued administration for 36 to 48 weeks showed the atrophy of the cells in the zones. Higher doses of BCP and phenylbutazone also produced the atrophy of the anterior lobe of hypophysis, the destruction of the follicular epithelia of thyroid gland and the atrophy of the lymphatic systems in the thymus and spleen.

The pregnant rats showed more sensitive to the toxic manifestation of BCP than the non-pregnant animals.

The difference in the toxic effects caused by the compound were quantitative but not qualitative between the pregnant and non-pregnant rats. Though the exact mechanism of hypersensitivity of the pregnant rats to BCP is not elucidated in the present experiments, the existence of gestation may burden the adrenocortical function and may facilitate the development of the decompensation caused by BCP. The minor teratogenic effect of BCP suggested that the adrenocortical stimulating action of the compound was not enough to induce the steroid effects on the offsprings. It is also worth mentioning that aminopyrine is not so much toxic on the pregnant rats compared with the non-pregnant ones, as shown in another series of experiments (8).

SUMMARY

The oral toxicity of 5-n-butyl-1-cyclohexyl-2,4,6-trioxoperhydropyrimidine (BCP) in the non-pregnant and pregnant rats was described in the present report.

1. The single oral administration of BCP (1.0–2.0 g/kg) caused the toxic effects such as depression of voluntary movement, marked reduction of food intake, conjunctival bleeding and profuse salivation. The cause of death presumably might be decompensation of the adrenocortical function.

2. The repeated treatment of BCP (200–800 mg/kg) for 7 days produced larger toxicity in the female rats than in the males. Histologically, the adrenal cortex of the dead animals caused by BCP showed diffuse hemorrhage accompanied with the feature of hyperfunction.

3. The pregnant rats showed more sensitive to the toxic manifestation of BCP than the non-pregnant females. BCP produced little teratogenic effect in the off-springs.

4. The chronic oral administration of BCP and phenylbutazone for 48 weeks showed more sensitive toxicity of both compounds in the females than in the males. BCP produced less sensitive chronic toxicity compared with phenylbutazone. Higher doses of both compounds resulted in the proliferation and bleeding of the adrenals followed by the atrophy.

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