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REPRODUCTIVE TOXICITY STUDIES WITH OXYBUTYNIN HYDROCHLORIDE

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SUMMARY

Oxybutynin hydrochloride, an anti-cholinergic/anti-spasmodic agent, was examined for its effect on fertility and peri-post natal development in the rat and its embryotoxic potential in the rat and rabbit. In the rat effects on reproductive performance included a slight increase in the incidence of foetal malformations, extended gestation period and impaired post natal performance of offspring. These findings occurred at dosages clearly associated with maternal toxicity. Oxybutynin hydrochloride did not exert an effect on reproductive processes in the rat at lower dosages or on embryonic and foetal development in the rabbit.

Key words: Oxybutynin; Anti-cholinergic/anti-spasmodic; Reproduction; Toxicity; Rat/rabbit

INTRODUCTION

Oxybutynin hydrochloride is a tertiary amine with the chemical name 4-diethylamino-2 butynylphenyl-cyclohexylglycolate hydrochloride. Besides showing a moderate anti-cholinergic action it also shows a papaverine-like spasmolytic action and in this respect differs from atropine and quaternary ammonium anti-cholinergic compounds [1,2]. Like certain other tertiary amines oxybutynin hydrochloride possesses local anaesthetic activity [3], but it has been found to be relatively free from central nervous system and cardiovascular side effects [1]. Clinically its intended usage is for treatment of smooth muscle disorders, in particular of the urinary tract, that is, neurogenic bladders and enuresis.

In the present investigation potential effects on reproduction were assessed by means of fertility and peri-post natal studies in the rat and by embryotox-

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icity studies in the rat and rabbit. The studies were performed during 1983. The study designs employed were based on concurrent requirements of the Japanese Ministry of Health and Welfare.

MATERIALS AND METHODS

1. General

Sprague—Dawley (CD) specific pathogen free rats and New Zealand White rabbits were maintained in a laboratory environment with controlled temperature, relative humidity, airflow and lighting. Diet (Spratts Laboratory Diet No 1 for rats and SDS Rabbit Diet SQC for rabbits) and water were freely available. Rabbits were housed individually. Rats were housed either individually, in pairs, or 4 per cage depending on study design and phase of study. Throughout the studies routine observation of parent animals comprised daily clinical signs, food consumption measurements and frequent recording of body weight on specified days; additionally in rat studies water consumption was recorded. At termination all animals were subject to macroscopic autopsy.

Days of gestation were designated taking the day on which a positive vaginal smear was detected (rat studies), or the day of observed mating (rabbit study), as Day 0 of gestation.

Oxybutynin hydrochloride was administered by gavage, as oral intake was the intended clinical route. The Sponsor had previously established that a 4% weight/volume aqueous solution was physically and chemically stable over 7 days. In the present studies dosing solutions were prepared daily using distilled water and were graded by serial dilution to allow use of constant dosage volumes of 10 ml/kg in all rat studies and 5 ml/kg in the rabbit study. The concentration of all solutions used was less than 4% weight/volume. Control animals were dosed with distilled water.

On one occasion in each of the main studies samples of the dosing solutions were sent for analysis by high performance liquid chromatography, with ultra violet detection at 220 nm, to confirm concentration of oxybutynin hydrochloride. Structural deviations among foetuses were categorized according to their severity and frequency of occurrence using the system evolved in these laboratories [4]. Namely, extremely rare and/or obviously detrimental deviations were classified as malformations, rare but not obviously detrimental deviations as anomalies, and common minor deviations as variants. Litter data were analysed statistically using the litter as the basic sample unit and non-parametric methods [5]. Analysis of variance was used for weekly body weight data and Fisher's Exact test [6] where appropriate.

2. Fertility study (Segment I design) in the rat

Twenty-four males/group were dosed for 9 weeks prior to mating through to termination, and 24 females/group were dosed for 2 weeks prior to mating and thereafter up to and including Day 7 of gestation. The animals were mated on a one to one basis. Females were killed on Day 20 of pregnancy.

Observations relating to reproductive capacity included mating performance, pregnancy rate, litter data at Day 20 of gestation and examination of foetuses for both visceral [7] and skeletal abnormalities [8].

3. Embryotoxicity study (Segment 2 design) in the rat

Thirty-six time-mated females/group were dosed from Day 7 to 17 of gestation inclusive. On Day 20 of gestation two-thirds were killed while the remaining animals were allowed to give birth and rear their young. Observations relating to reproductive capacity included litter data at Day 20, examination of foetuses, gestation period, pre-weaning development (incisor eruption, startle response, eye opening, air righting reflex, pupil reflex) and litter data through to weaning. Also, an F_1 generation was derived and reared to maturity with observation of growth, behaviour (Hole-board [9], Inclined Plane [10] and Passive Avoidance tests [11]) and reproductive performance.

4. Embryotoxicity study (Segment 2 design) in the rabbit

Sixteen time-mated females/group were dosed from Day 6 to 18 of gestation inclusive. On Day 29 they were killed, litter values determined and foetuses examined for macroscopic visceral abnormalities. All foetuses were processed for subsequent skeletal examination.

5. Peri-post natal study (Segment 3 design) in the rat

Twenty-four time-mated females/group were dosed from Day 17 of gestation through to Day 21 post partum. All females were allowed to litter. Observations relating to reproductive capacity included gestation period, litter data through to weaning, pre-weaning development and performance of an untreated F_1 generation.

6. Dosage selection

Preliminary investigations were performed initially in both species with treatment periods based on the duration of treatment in the main studies. Only females were used in the rabbit preliminary study whereas in the rat both sexes were employed; effects on pregnancy were not investigated.

Based on findings in the rabbit preliminary study it was anticipated that 50 mg/kg per day, or thereabouts, would elicit an appropriate degree of maternal toxicity for use as the high dosage in the main study. Based on the rat preliminary investigation 100 mg/kg per day was selected as the high dosage for the Segment 2 and 3 studies and 75 mg/kg per day for the Segment 1. The lower top dosage was selected for the longer Segment 1 study as body weight retardation in the preliminary study persisted throughout treatment. The high dosage for the Segment 3 study was subsequently revised to 50 mg/kg per day due to findings at parturition in the rat Segment 2 study.

Low and intermediate dosages were selected for the main studies bearing in mind the anticipated clinical dosage (approx. 0.2 mg/kg per day) and that body weight differences in the rat preliminary study indicated a shallow dose-effect curve. The dosage sequences used are indicated in Table I.

TABLE I

DOSAGE SEQUENCES

Species	Study	Dosages (mg/kg/day)
Rabbit	Segment 2	0, 3, 12 and 48
Rat	Segment 1	0, 3, 15 and 75
	Segment 2	0, 4, 20 and 100
	Segment 3	0, 4, 20 and 50 (100)[a]

[a]100 mg/kg per day originally selected but subsequently revised.

RESULTS

1. Segment 1 study in the rat

Dosages: 0, 3, 15 and 75 mg/kg per day. At 75 mg/kg per day signs of reaction to treatment comprised of mydriasis, which was consistent with oxybutynin hydrochloride showing anti-cholinergic activity, and increased salivation. Males also showed brown facial staining. Three males died, compared with one in the control group, but no consistent macroscopic changes were observed at autopsy. Among both males and females water consumption was increased and food consumption slightly increased. Mean body weight gain among males was retarded throughout (Fig. 1), while females were unaffected other than for a slight impairment during early gestation (Table II). Mating performance and pregnancy rate were unaffected by treatment. A single female showed total resorption but in isolation there was no obvious treatment relationship. There were no effects upon litter data (Table III) or incidences of malformations (Table IV). Although incidences of visceral and skeletal anomalies and of sternebral variants were higher than in the concurrent control group there were no statistically significant differences. Also, all values were within the control range derived from 6 closely contemporaneous studies performed in these laboratories using the same strain of rat. In contrast to these negative findings, however, the incidence of litters with one or more foetuses showing supplementary thoraco-lumbar ribs (i.e. unilateral or bilateral 14th rib) was significantly increased (Table IV).

At 3 and 15 mg/kg per day mean weight gains of males were marginally lower than among control animals but differences were not statistically significant. Increased salivation and mydriasis were observed among males at 15 mg/kg per day, and occasional males at 3 mg/kg per day showed increased salivation. There were no effects upon reproduction at either dosage that were considered attributable to treatment.

2. Segment 2 study in the rat

Dosages: 0, 4, 20 and 100 mg/kg per day. Treatment at 100 mg/kg per day induced increased salivation, mydriasis and brown facial staining, increased water consumption (Fig. 2), marginally reduced food consumption and

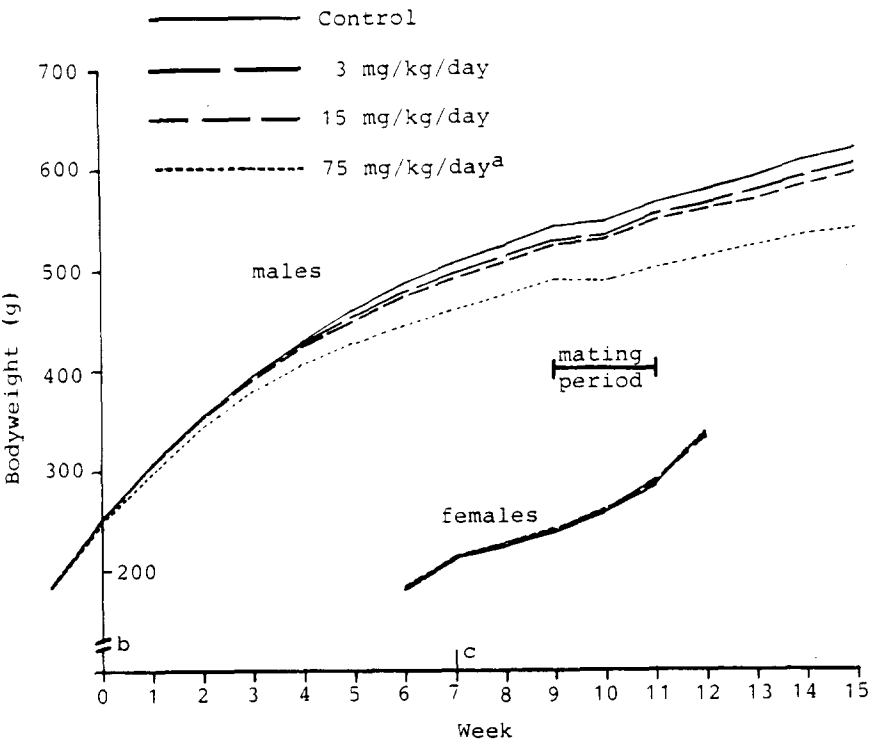

Fig. 1. Group mean weekly body weights, rat Segment I study. [a]Weight gain of males significantly reduced, Anovar $P < 0.01$. [b,c]Commencement of treatment, respectively, for males and females.

reduced body weight gain (Table II). Among dams sacrificed on Day 20 of gestation there were no adverse effects upon litter size, post implantation loss, litter and mean foetal weights (Table III), incidences of visceral and skeletal anomalies or of sternebral variants (Table IV). However, the incidence of malformed foetuses was increased, mainly due to the occurrence in separate litters of 3 foetuses with interventricular septal defects (Table V). The incidence of litters with one or more pups showing extra thoraco-lumbar ribs was also significantly increased (Table IV). Among dams allowed to litter the mean duration of gestation was increased (Table VI). Four dams showed dystocia as indicated by delayed birth in conjunction with signs including prolonged vaginal bleeding and pallor of eyes and extremities. Of these 4 dams, 1 died, 1 was killed and 2 that survived showed total litter loss at birth. Among other dams pup mortality at birth was increased and further losses occurred between birth and Day 4 post partum although to a lesser extent. Reflecting these losses, litter size and litter weight were reduced (Table VI). Among surviving young there was no adverse effect upon pup weight which at birth was slightly greater than the control value, probably reflecting the longer gestation period. There were no adverse effects upon pre-weaning

TABLE II

MEAN BODY WEIGHT CHANGES OF FEMALES DURING PREGNANCY AND POST PARTUM

Weight change interval, Days[a]	Weight change (g) at dosage (mg/kg/day)[b] 0	3	15	75
Rat Segment 1 study				
0—8G	31	33	32	28
0—20G	131	121	123	135
	0	4	20	100
Rat Segment 2 study				
7—10G	19	18	15	0
7—17G	78	79	70	55
7—20G	122	126	116	104
7G—0P	55	54	48	33
7G-21P	70	67	72	57
	0	3	12	48
Rabbit Segment 2 study				
6—10G	74	80	72	7
6—19G	292	278	284	210
6—29G	471	540	435	467
	0	4	20	50
Rat Segment 3 study				
17—20G	33	31	28	20
17G—0P	−39	−42	−48	−55
17G—14P	4	6	−6	−21
17G—21P	−7	−15	−20	−29

[a]G = Days of gestation; P = Days post partum.
[b]Animals showing total litter loss excluded from calculations.
Baseline for weight change calculations corresponds to the start of treatment.

development as indicated by values for specified developmental stages, or on post weaning development, behaviour and subsequent reproductive capacity of the selected animals.

At 20 mg/kg per day increased salivation and mydriasis were observed and food consumption and weight gain of dams were slightly lower than among control animals. At 4 mg/kg per day the maternal response was limited to increased salivation affecting occasional animals.

At and below 20 mg/kg per day there were no adverse effects upon the gestation periods of dams allowed to litter or upon the litter parameters either at Day 20 of gestation or from birth through to weaning. There were

TABLE III

LITTER VALUES AT GESTATION SACRIFICES

Observation	Mean values[a] at dosage (mg/kg/day)				
	0	3	15	75	
Rat Segment 1 study					
No of pregnant dams	21	21	23	18	(19)
Litter size	13.7	12.5	12.3	13.2	(12.5)
Losses (%)					
pre-implantation	4.8	13.4	12.4	8.4	(12.2)
post implantation	4.2	4.4	6.7	6.7	(11.6)
Litter weight (g)	45.90	41.34	40.62	43.92	
Foetal weight (g)	3.35	3.24	3.32	3.34	
	0	4	20	100	
Rat Segment 2 study					
No. of pregnant dams	23	22	22	23	
Litter size	11.5	11.5	11.8	10.8	
Losses (%)					
pre-implantation	7.9	9.5	5.7	7.8	
post implantation	1.3	5.6	4.3	6.2	
Litter weight (g)	40.80	39.88	40.54	39.51	
Foetal weight (g)	3.55	3.49	3.43	3.69	
	0	3	12	48	
Rabbit Segment 2 study					
No. of pregnant dams	14	16	13	15	(16)
Litter size	7.1	8.1	7.5	9.3	(8.8)
Losses (%)					
pre-implantation	15.5	14.5	10.5	9.3	(9.3)
post implantation	19.8	14.7	15.6	4.9	(10.9)
Litter weight (g)	304.4	342.0	310.8	365.9	
Foetal weight (g)	44.0	44.0	43.4	39.9	

No statistically significant differences, Kruskal-Wallis and Jonckheere tests, $P > 0.05$.
[a]Values in parentheses calculated including single females showing total resorption or abortion.

no obvious treatment related effects upon the incidence of foetal malformations although 1 foetus at 20 mg/kg per day showed interventricular septal defect and single foetuses at both dosages showed situs inversus (Table V). There was no adverse effect upon incidences of anomalies or skeletal variants, or upon pre-weaning development and the performance of the F_1 generation reared to maturity.

3. Segment 2 study in the rabbit

Dosages: 0, 3, 12 and 48 mg/kg per day. Animals dosed at 48 mg/kg per

TABLE IV

FOETAL EXAMINATION DATA

Observation	Percentage incidences at dosage (mg/kg/day)			
	0	3	15	75
Rat Segment 1 study				
Malformations				
litters affected[a]	5.0 (1/20)	0.0 (0/21)	0.0 (0/23)	0.0 (0/18)
foetuses affected	0.3	0.0	0.0	0.0
Visceral anomalies	2.3	6.0	3.5	6.6
background prevalence[b]	Mean 5.5,	Low range 0.0,	High range	10.1
Skeletal anomalies	8.8	8.5	16.7	20.9
background prevalence[b]	Mean 13.6,	Low range 8.3,	High range	21.3
Sternebral variants	58.2	86.2	63.3	72.1
Foetuses with extra ribs[a,c]	0.0 (0/19)	2.8 (2/17)	0.6 (1/22)	4.6 (4/18*)
	0	4	20	100
Rat Segment 2 study				
Malformations				
litters affected[a]	0.0 (0/23)	9.1 (2/22)	9.1 (2/22)	21.7 (5/23*)
foetuses affected	0.0	0.8	0.8	3.6
Visceral anomalies	3.3	3.3	3.3	3.0
Skeletal anomalies	13.4	7.6	17.9	11.0
Sternebral variants	58.7	59.2	65.4	47.0
Foetuses with extra ribs[a]	0.0 (0/23)	0.9 (1/22)	0.0 (0/22)	6.6 (7/22**)
	0	3	12	48
Rabbit Segment 2 study				
Malformations				
litters affected[a,d]	14.3 (2/14)	0.0 (0/16)	46.2 (6/13)	13.3 (2/15)
foetuses affected	2.2	0.0	5.3	1.4
Visceral anomalies	2.8	1.8	0.8	5.3
Skeletal anomalies	29.5	8.4	19.4	15.2
Sternebral variants	16.0	22.1	25.7	17.1
Foetuses with extra ribs	50.0	32.2	43.8	49.7

[a]Numbers of affected litters indicated in parentheses.
[b]Data derived from 6 recent prior embryotoxicity studies.
[c]Some litters excluded from analysis — correct day of sacrifice not predicted due to ambiguous vaginal smear data.
[d]Data not statistically analysed in absence of dosage relationship.
Difference from control statistically significant at Fisher's Exact test: $*P < 0.05$, $**P < 0.01$.

day showed mydriasis and lethargy, and food consumption and weight gain (Table II) were reduced. At 12 mg/kg per day occasional animals showed mydriasis and lethargy. Treatment had no apparent adverse effect upon litter values (Table III) or upon embryonic and foetal development as assessed by

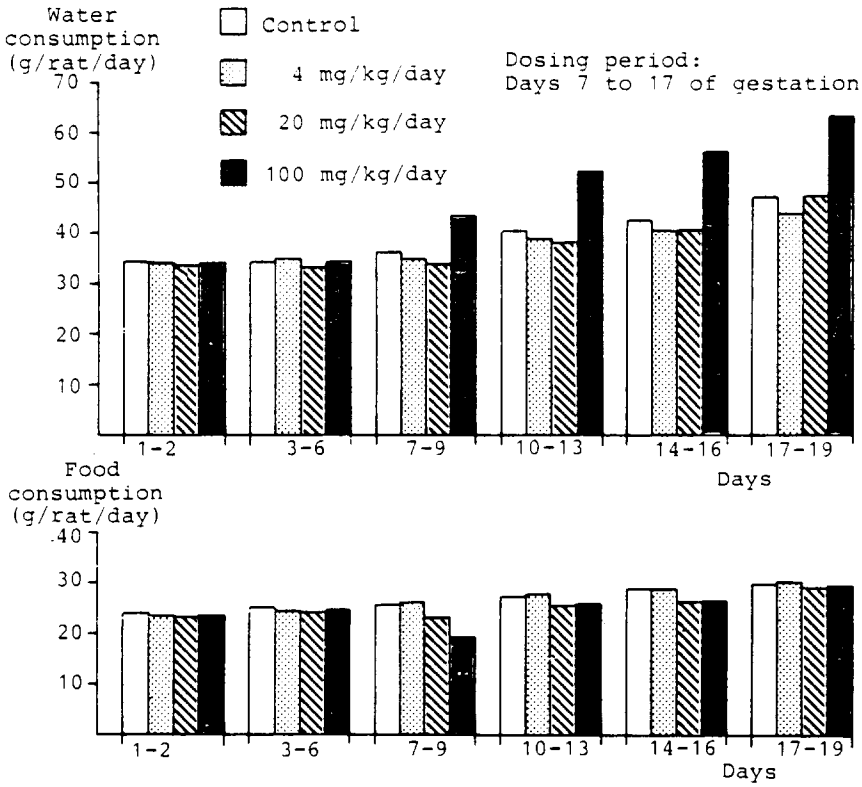

Fig. 2. Group mean food and water consumption, rat Segment 2 study.

the incidence of malformations, anomalies and skeletal variants (Table IV), at any dosage.

4. Segment 3 study in the rat

Dosages: 0, 4, 20 and 50 mg/kg per day. Treatment at 50 mg/kg per day was associated with increased post dosing salivation, mydriasis and brown facial staining. Water consumption, food consumption and weight gain (Table II) were reduced but there was no effect on the mean duration of gestation (Table VI). A single dam showed total litter loss at birth and among other dams pup mortality between birth and Day 4 post partum was slightly increased. Post partum weight gain to weaning was reduced and the occurrences of pinna unfolding, startle response and eye opening were all marginally delayed (Table VII). Following weaning the body weight of selected males remained lower than that of the controls and at 6 weeks of age, although there were no adverse effects on values for the inclined plane or passive avoidance tests, they showed reduced mobility and rearing activity in the hole-board test. However, when the latter test was repeated at 9 weeks of age their performance was similar to that of controls. Following weaning, selected females showed body weight recovery and performed similarly to controls in all three post weaning behaviour tests.

TABLE V

COMPARISON OF MALFORMATIONS OBSERVED IN RAT SEGMENT 2 STUDY WITH BACKGROUND CONTROL DATA

Malformation	Prevalence of litters with ⩾ 1 pup affected[a]				
	Background data[b]	At dosage of oxybutynin hydrochloride (mg/kg/day)			
		0	4[c]	20	100[c]
Any malformation	34/454 (7.5)	0/23 (0.0)	2/22 (9.1)	2/22 (9.1)	5/23* (21.7)
range	(0.0—13.6)				
Interventricular septal defect (IVSD)	5/454 (1.1)	—	0/22 (0.0)	1/22 (4.5)	3/23* (13.0)
range	(0.0—4.3)				
Situs inversus (SI)	3/454 (0.7)	—	1/22 (4.5)	1/22 (4.5)	1/23[d] (4.3)
range	(0.0—4.5)				
IVSD or SI	7/454 (1.5)	—	1/22 (4.5)	2/22 (9.1)	3/23** (13.0)
range	(0.0—4.5)				

[a]Values in parentheses indicate percentage of affected litters.
[b]Data derived from 20 embryotoxicity studies performed between January 1982 and March 1983.
[c]Non-cardiac malformations observed: 4 mg/kg per day, one foetus showing gastroschisis and multiple skeletal defects; 100 mg/kg per day, one foetus showing hydrocephaly and microphthalmia, second foetus showing bilateral forelimb flexure.
[d]Affected foetus also showing IVSD.
Differences from background control data statistically significant at Fisher's Exact test: *$P < 0.05$, **$P < 0.01$.

TABLE VI

GESTATION PERIODS AND LITTER VALUES AT WEANING

Observation	Mean values[a] at dosage (mg/kg/day)					
	0	4	20		100	
Rat Segment 2 study						
No. of pregnant dams[b]	12	12	12		7	(9)
Gestation period (days)	21.5	21.7	21.8		23.2*	
Litter size	10.6	11.6	10.3		7.4	(5.8*)
Cumulative pup loss (%)	4.0	3.5	3.0		31.1**	(46.4***)
Litter weight (g)	471.8	503.2	490.4		350.8	
Mean pup weight (g)	44.8	43.6	48.3		48.4	
	0	4	20		50	
Rat Segment 3 study						
No. of pregnant dams	24	25	24	(25)	24	(25)
Gestation period (days)	21.5	21.8	21.7		21.3	
Litter size	10.9	11.2	10.5	(10.0)	9.7	(9.3)
Cumulative pup loss (%)	6.9	3.6	5.8	(9.5)	19.2	(22.4)
Litter weight (g)	435.1	456.9	403.7		327.8**	
Mean pup weight (g)	40.2	41.5	39.1		33.8*	

[a]Values in parentheses calculated including females showing total litter loss.
[b]Excludes 2 dams at 100 mg/kg per day showing dystocia/death.
Differences from control statistically significant at Kruskal-Wallis test (litter data) or Fisher's Exact test (gestation period data): $*P < 0.05$, $**P < 0.01$, $***P < 0.001$.

At 20 mg/kg per day animals showed increased post dosing salivation and mydriasis. Lower values for water and food consumption were recorded but not consistently; body weight gain was slightly reduced. At 4 mg/kg per day the only evidence of reaction to treatment was increased post dosing salivation among occasional parent females.

At and below 20 mg/kg per day there were no obvious adverse effects upon the duration of gestation, upon the litter parameters from birth through to weaning, including the attainment of the specified pre-weaning developmental stages, or upon post weaning growth and behaviour. In the absence of any general effect upon litter data, the occurrence of a single total litter loss at 20 mg/kg per day was considered coincidental.

At all dosages investigated, pregnancy rate and litter data of the F_1 generation appeared unaffected by the treatment of the F_0 dams.

DISCUSSION

In the rat Segment I study there was no effect on mating performance or pregnancy rate and differences among offspring were confined to an increased incidence of foetuses with extra thoraco-lumbar ribs at the high dosage of

TABLE VII

DATA FOR F_1 GENERATION IN RAT SEGMENT 3 STUDY

Observation	Mean values at dosage (mg/kg/day)			
	0	4	20	100
Age (days)[a] for:				
pinna unfolding	25.0	25.1	25.2	25.4*
startle response	35.0	34.9	35.1	35.6*
eye opening	36.3	36.2	36.5	36.9***
Holeboard test (counts); males at 6 weeks age[b]:				
hole exploration	29	31	30	28
open field activity	124	138	127	107*
rearing	41	47	39	33*
Holeboard test (counts); males at 9 weeks age[b]:				
hole exploration	11	10	8	10
open field activity	108	131	101	107
rearing	48	52	40	44
Weights (g) at week of age[b]:				
4, males	78	79	77	66
females	74	73	71	63
12[c], males	451	443	432	409**
females	252	255	258	252*

[a]For pre-weaning developmental stages post coital age was used in these studies in view of longer gestation period in the rat Segment 2 study.
[b]Ages quoted refer to nominal post partum age.
[c]Statistical analysis performed using weight gains between nominal weeks 4 and 12.
Differences from control statistically significant at Kruskal-Wallis test (developmental/behavioural data) or at Anovar (weight gain): $*P < 0.05$, $**P < 0.01$, $***P < 0.001$.

75 mg/kg per day. Although the occurrence of extra ribs has been reported for a large number of chemical agents that do not cause malformation, their occurrence has been demonstrated for several compounds that do [12]. In the study design that was employed, although treatment was discontinued on Day 7 of gestation, the possibility of direct compound effects on organogenesis cannot be excluded, especially as in the Segment 2 study effects upon the parent female (dystocia/extended gestation) were apparent 4—5 days after treatment ceased. However, in the present Segment I study no malformations were observed at 75 mg/kg per day and the increased incidence of extra ribs occurred in association with maternal effects and hence conceivably may have been an indirect rather than a direct effect of treatment. Irrespective of which may be the case, there was no clear indication of the foetus being adversely affected by treatment at a lower dosage than was the adult.

In the rat Segment 2 study effects on reproductive performance were

observed at the high dosage of 100 mg/kg per day. Possibly reflecting a spasmolytic action of oxybutynin hydrochloride on the uterus, some dams showed dystocia, and the mean duration of gestation was extended. As might be expected with such an effect, immediate post natal mortality was increased; however, whether or not the effect of gestation was the sole cause of the increased losses was uncertain. Among dams sacrificed during gestation there was no adverse effect upon post-implantation loss or foetal weight but there was an increased incidence of foetuses with interventricular septal defect and of foetuses with extra thoraco-lumbar ribs. However, these findings occurred at a dosage associated with a clear retardation in maternal weight gain. At 4 and 20 mg/kg per day there were no clear effects on reproductive performance. One possible discrepancy was the low incidence of foetuses with malformation involving the heart, which was of interest due to the increased incidence at 100 mg/kg per day. However, the incidences at 4 and 20 mg/kg per day of both total malformations and individual types of malformation were within the background control range, and the incidence of interventricular septal defect was confined to a single affected foetus at 20 mg/kg per day. The absence of an effect upon the foetus at these 2 dosages was further supported by the absence of other structural changes, such as supplementary ribs as observed at 100 mg/kg per day, and by the absence of any adverse effect upon the survival and growth of offspring.

In the corresponding Segment 2 study in the rabbit there was no obvious indication of an effect upon embryo-foetal development, despite the occurrence of maternal effects at the high dosage of 48 mg/kg per day.

At the high dosage of 50 mg/kg per day, animals in the rat Segment 3 study showed no evidence of dystocia or extended gestation period as was observed in the rat Segment 2 study. The absence of this effect probably reflected the lower dosage used, although the difference in dosing period may also have been a factor. Pup mortality in the Segment 3 study was slightly increased at 50 mg/kg per day and pup weight gain clearly reduced. Possibly correlating with the lower pup weights, 3 of the pre-weaning developmental parameters were slightly delayed; selected male offspring, but not females, also showed a continuation of the lower weight gain beyond weaning. Once again, however, all of these findings occurred in association with effects upon the maternal animal. Also, at the intermediate dosage of 20 mg/kg per day there was no apparent effect on litter data despite a slight retardation in maternal weight gain.

From the various studies with oxybutynin hydrochloride the overall weight of evidence suggested that the effects on reproductive processes observed in the rat only occurred at dosages associated with obvious indications of a general reaction to treatment such as effects upon food and water consumption, and body weight gain. Effects on reproductive processes were judged to be absent at lower dosages despite the occurrence of signs of pharmacological activity (mydriasis). The no observable effect levels for reproductive processes in the rat and, more specifically, for embryo-foetal development in the rabbit were therefore considered to be 20 and 48 mg/kg per day respectively.

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