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Embryotoxicity of Sex Steroidal Hormones in Nonhuman Primates: II. Hydroxyprogesterone Caproate, Estradiol Valerate

A.G. HENDRICKX, R. KORTE, F. LEUSCHNER, B.W. NEUMANN, A. POGGEL, P. BINKERD, S. PRAHALADA, AND P. GÜNZEL
California Primate Research Center, University of California, Davis, California 95616 (A.G.H., P.B., S.P.); Hazleton Laboratories, Hazleton Germany, Kesselfield 29, D-4400 Munster (R.K.), Laboratory for Pharmacology and Toxicology, D-2104 Hamburg 92 (F.L., B.W.N.), and Research Laboratories of Schering AG, Pharma Forschung/FB III, Berlin/Bergkamen, D-1000 Berlin 65 (A.P., P.G.), Federal Republic of Germany

ABSTRACT Two sex steroid compounds which have been used clinically for parenteral supportive therapy of pregnancy were examined for embryotoxic effects in rhesus and cynomolgus macaques. Hydroxyprogesterone caproate (HPC) alone or in combination with estradiol valerate (EV) were administered intramuscularly (i.m.) to pregnant monkeys at 7-day intervals between 20 and 146 days of gestation and fetuses were examined following cesarean section at 150 ± 2 days. HPC alone was tested in both species at doses ranging from 0.01× to 10× the human dose equivalent (HDE); only rhesus monkeys were exposed to the HPC + EV combination at 0.1× to 10× HDE. Total embryolethality resulted following the administration of HPC alone and combined with EV at 1× and 10× HDE in rhesus monkeys; the level of abortions in cynomolgus monkeys exposed to HPC (0.1× to 1× HDE) was comparable to controls. A small number of nonspecific malformations and developmental variations observed in cynomolgus fetuses after HPC exposure were considered to be incidental findings. No anomalies were found in surviving rhesus monkey fetuses treated with HPC + EV. The results indicate that long-term in utero exposure to the progestin, HPC, alone or in combination with EV in rhesus and cynomolgus monkeys, is embryolethal but not teratogenic at doses up to ten times the human therapeutic dose.

For the last several decades there has been much concern over the association of exogenous hormone therapy and a variety of birth defects. Worldwide clinical uses of female sex hormones include oral contraception, oral pregnancy tests, treatment for habitual or threatened abortion, and antineoplastic therapy. Much attention has been directed toward the potential teratogenicity during early pregnancy of combined estrogens and progestins, natural or synthetic, delivered as oral contraceptives and oral pregnancy tests in both human and animal studies (Lalit Ambani et al., '77; Briggs and Briggs, '79; Schardein, '80; Wilson and Brent, '81; Katz et al., '85; Hendrickx et al., '87), while there has been less concern about the long-term use of either natural or synthetic estrogens or progestins, administered singly or in combination, as a therapy for habitual or threatened abortion.

The nonhuman primate is an appropriate model for the evaluation of potential embryotoxic effects because of its similarity to the human in reproductive physiology, placentation, developmental timetables, and especially the extended period of gestation (5.5–6 months) compared to other common laboratory species. Only limited studies on the embryotoxicity of sex hormones have been reported in nonhuman primates. The administration of androgens during the critical phase of genital development causes abnormalities of the external genitalia in rhesus monkeys (Van Wagenen and Hamilton, '43; Wells and Van Wagenen, '54; Goy et al., '77). Similar observations have been well documented in women, and thus the use of known androgens in women is discouraged therapeutically.

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Estrone, estradiol dipropionate, hydroxyprogesterone caproate (HPC), and progesterone were found to have no adverse effects on the prenatal rhesus monkey (Van Wagenen and Morse, '44; Wharton and Scott, '64; Courtney and Valerio, '68). On the other hand, exposure to the following hormones during pregnancy is associated with embryotoxicity in various primate species: diethylstilbestrol—genital defects (Hendrickx et al., '79; Thompson et al., '81; Johnson et al., '81; Johnson, '84); norethindrone—embryolethality, genital defects, and growth retardation (Wharton and Scott, '64; Prahalada and Hendrickx, '83; Hendrickx et al., '87); and medroxyprogesterone acetate—genital and adrenal defects (Prahalada et al., '85a,b).

The objective of this study was to evaluate the embryotoxicity of HPC alone or in combination with estradiol valerate (EV) administered during the embryonic and fetal period in macaques. Both of these treatments have been used for supportive therapy during human pregnancy.

MATERIALS AND METHODS

The rhesus monkey (*Macaca mulatta*) was chosen as the original test species; however, due to a ban on exportation and the subsequent limited availability of this species over the course of the study, the cynomolgus monkey (*Macaca fascicularis*) was also utilized. The studies were carried out in the Laboratory for Pharmacology and Toxicology in Hamburg and the Hazleton Laboratories Germany in Münster-Hiltrup, Federal Republic of Germany. During the course of the experiment all the animals were maintained in individual cages which conformed to the guidelines for laboratory animal care for the Federal Republic of Germany. The animal quarters were maintained at 76–80°F and 45% humidity and artificial lighting was provided between 7:00 A.M. and 7:00 P.M. Commercial monkey chow containing 15–25% protein was provided twice daily with occasional fruit supplementation, and water was provided ad libitum. Adult sexually mature female rhesus and cynomolgus macaques weighing 6–10 kg and 2–5 kg, respectively, were used. All females had a history of regular menstrual cycles and menstruation was detected by daily swabbing of the vagina and examination of the cage for blood. The rhesus and cynomolgus females were mated with proven fertile males for 2–8 hours per day on 2 days between days 11 and 15 of the menstrual cycle with the first day of menstrual bleeding considered as day 1 of the cycle. A successful mating was indicated by the presence of spermatozoa in a vaginal smear at the end of the mating period. The day on which sperm were found in the vaginal smear was considered day 0 of pregnancy.

Pregnancy was detected in both species by the mouse uterus test on serum samples collected on days 18 and 19 of pregnancy and by bimanual rectal palpation of the uterus (Wilson et al., '70). Blood samples were also collected and stored to confirm pregnancy by serum progesterone levels retrospectively. After confirmation of pregnancy, the females were randomly assigned to different experimental groups. The details of the animals and the treatment schedules used are presented in Tables 2 and 3.

Pregnant rhesus monkeys received intramuscular (i.m.) doses of hydroxyprogesterone caproate (HPC) and estradiol valerate (EV) at doses which ranged from 0.01× to 10× the human dose equivalent (HDE). Hydroxyprogesterone caproate alone was administered intramuscularly to pregnant rhesus and cynomolgus monkeys at 0.1× to 10× HDE. It was necessary to use the cynomolgus monkey to test intermediate dosages of this drug following the initial study in rhesus monkeys due to the limited availability of the latter species. Both treatments were administered once a week between gestational days (GD) 20 and 146 to mimic a supportive hormonal therapy of weekly injections during the entire period of pregnancy in humans. Each experiment had a concurrent control group which received injections of the solvent on the same treatment schedule.

All animals were weighed before administration of the drug and at regular intervals during treatment. Average maternal weights ($\bar{X} \pm$ S.D.) were comparable for females randomly assigned to the treatment groups (Table 1). The pregnant animals were observed regularly for adverse clinical signs (vomiting, diarrhea, lethargy), food intake, and vaginal bleeding during the period of study.

Fetuses were delivered by cesarean section at 150 ± 2 days. Immediately after delivery, all fetuses were weighed, morphometrically measured, and examined for malformations by using standard protocols. The brain was removed, examined, weighed, and fixed in 10% buffered formalin. All visceral organs were examined in situ prior to removal, at which time they were further examined, weighed,

TABLE 1. Maternal body weights (kg) during treatment

Compound/species	Initial weight[1]	Final weight[2]	Weight change[3]
HPC + EV[4]			
Rhesus monkeys			
Control	5.7 ± 0.9[5]	6.7 ± 0.7	1.0 ± 0.6
0.01×	6.3 ± 1.3	6.9 ± 1.3	0.6 ± 0.3
0.1×	5.9 ± 1.1	6.9 ± 1.5	1.3 ± 0.7
0.33×	6.6 ± 1.2	7.5 ± 1.6	0.9 ± 0.6
Control	5.2 ± 0.3	5.7 ± 0.2	0.5 ± 0.2
1×	4.5 ± 0.7	4.3 ± 0.7	−0.3 ± 0.6*
10×	5.2 ± 0.4	5.2 ± 0.6	−0.1 ± 0.2*
HPC			
Rhesus monkeys			
Control	5.2 ± 0.3	5.7 ± 0.2	0.5 ± 0.2
1×	5.3 ± 0.5	5.5 ± 0.6	0.2 ± 0.7
10×	5.2 ± 0.5	5.0 ± 0.6	−0.2 ± 0.3*
Cynomolgus monkeys			
Control	2.9 ± 0.4	3.9 ± 0.6	1.0 ± 0.3
0.1×	2.8 ± 0.3	3.8 ± 0.5	1.1 ± 0.3
0.33×	3.1 ± 0.5	4.1 ± 0.5	0.9 ± 0.2
1.0×	2.9 ± 0.4	4.2 ± 0.3	1.2 ± 0.2

[1]Pretreatment weight.
[2]Weight prior to c-section.
[3](Final-initial) weight.
[4]Hydroxyprogesterone caproate plus estradiol valerate.
[5]$\bar{X}$ ± SD.
*$P < .05$.

TABLE 2. Embryotoxicity of HPC + EV

Species	HDE[1]	No. of pregnancies[2]	Embryolethality (%)	No. of fetuses	Fetal weight (gm) ($\bar{X}$ ± SD)	Anomalies
Rhesus monkey	Control	15	2 (13)	13	347.5 ± 56.8	0
	0.01×	8	3 (38)	5	348.0 ± 64.4	0
	0.1×	9	3 (33)	6	352.8 ± 75.3	0
	0.33×	10	3 (30)	7	360.6 ± 51.1	0
	1×	10	10 (100)*	0	—	—
	10×	10	10 (100)*	0	—	—

[1]HDE = human dose equivalent based on approximate human dose of 10.0 mg/kg HPC and 0.2 mg/kg EV.
[2]Treated (i.m.) at 7-day intervals between days 20 and 146 of gestation.
*$P < .005$.

TABLE 3. Embryotoxicity of HPC

Species	HDE[1]	No. of pregnancies[2]	Embryo-lethality (%)	No. of fetuses	Fetal weight (gm) ($\bar{X}$ ± SD)	Anomalies
Rhesus monkey	Control	8	0	8	339.4 ± 62.8	0
	1×	10	10 (100)*	0	—	—
	10×	10	10 (100)*	0	—	—
Cynomolgus monkey	Control	10	3 (30)	7	318.5 ± 32.3	0
	0.1×	10	2 (20)	8	291.1 ± 31.1	0
	0.33×	10	4 (40)	6	304.6 ± 30.2	0
	1×	10	4 (40)	6	306.7 ± 50.5	1[3]

[1]HDE = human dose equivalent based on approximate human dose of 10.0 mg/kg HPC.
[2]Treated (i.m.) at 7-day intervals between days 20 and 146 of gestation.
[3]Unilateral microphthalmia and skeletal defects.
*$P < .005$.

and fixed in 10% buffered formalin. The external genitalia were examined in detail for abnormalities, dissected in toto, and fixed. The skeletons were fixed in 10% buffered formalin and stained with Alizarin Red S.

The incidence of embryotoxicity (lethality and malformation) for each treated group was compared to the concurrent control group by means of Fisher's Exact Test (Finney et al., '63). Fetal and maternal weight data for each experiment were statistically analyzed by using the General Linear Models for unbalanced analysis of variance (SAS Statistical Program, Cary, ND) and the Tukey studentized range test.

RESULTS

Of the five dose levels of HPC + EV studied in the rhesus monkey, total embryolethality was observed at the two highest doses (1× and 10×) and similar moderate rates of embryolethality were observed in the other three treatment groups (0.01×, 0.1×, and 0.33×) (Table 2). Abortions/resorptions occurred between gestational days 57 and 112. Untimed pregnancy losses were confirmed by palpation or cesarean section later in pregnancy. No anomalies were found in any of the surviving fetuses examined at cesarean section. All fetal weights and measurements were within the normal range for control fetuses.

When HPC alone was given, total embryolethality was observed at both the low (1×) and high (10×) doses in the rhesus monkey (Table 3). A consistently moderate level of embryo/fetal death was observed in cynomolgus monkeys at all dose levels (0.1×, 0.33×, and 1×) as well as in the controls. The time for detection of abortion/resorption, accomplished by periodic uterine palpation or by cesarean section, varied from as early as 30 days to as late as 146 days gestation.

The incidence of malformations was very low after HPC treatment (Table 3). Nongenital malformations were only observed in one dead cynomolgus monkey fetus at the high dose level (1× HDE). This fetus, examined at GD 146, had a small right eye (microphthalmic), fused ribs, and fused asymmetrical vertebral bodies in the upper thoracic region (ribs 1–5 and thoracic vertebrae 1–6). Minor skeletal and genital variations were observed in both treated and control cynomolgus fetuses. No differences between control and treated fetal weights and measurements were observed in cynomolgus monkeys following HPC treatment.

No signs of maternal toxicity were observed in cynomolgus monkeys following HPC treatment; however, there was a significant reduction ($P < .05$) in maternal weight gain in rhesus monkeys treated with 1× and 10× HDE HPC + EV and 10× HDE HPC alone.

DISCUSSION

This study has demonstrated embryolethality as the primary embryotoxic effect following in utero exposure to HPC alone or in combination with EV in rhesus and cynomolgus monkeys. Both treatments elicited a steep dose-response effect in rhesus monkeys with total embryolethality occurring at the approximate human doses. Cynomolgus monkeys were not as sensitive to these embryolethal effects at lower or equivalent human therapeutic doses (0.1×–1×) of HPC. The malformations observed in one cynomolgus monkey after 1× HDE HPC are considered to be of spontaneous origin rather than a drug-related response.

The absence of masculinization in female fetuses exposed to HPC confirms the results reported in mice (Seegmiller et al., '83), rats (Jung and Peters, '67), and rhesus monkeys (Courtney and Valerio, '68). Moreover, HPC, which is classified as a "pure" progestogen with a depot effect, possesses neither androgenic nor estrogenic properties (Neumann, '78; Kessler and Borman, '58).

Due to the high level of embryo or fetal death, less than half of the treated fetuses in both studies were available for morphological examination. That embryolethality masked teratogenicity following exposure to these compounds cannot be ruled out; however, based on the minor, nonspecific defects which were observed in surviving fetuses, it is unlikely that intrauterine death was secondary to severe malformation, as has been suggested by some investigators (Beck and Lloyd, '63; Wilson, '59). Rather, embryolethal effects and teratogenic effects are interpreted as being unrelated embryotoxic responses under these experimental condi-

tions. Although the pathogenesis of embryonic death associated with in utero exposure to sex steroids has not been clarified, an imbalance in the feto-maternal endocrine relationship or a disorder in placental circulation has been hypothesized (Jung and Peters, '67).

Various combinations of natural and/or synthetic progestins and estrogens have been studied in laboratory animals and have been reviewed elsewhere (Hendrickx et al., '87). In the one study reporting the effects of HPC and estradiol benzoate in laboratory animals Jung and Peters ('67) observed embryolethality and growth retardation, but no teratogenicity after fetal exposure to this hormonal combination during pregnancy in the rat. Numerous studies have also been done in laboratory animals to assess the embryotoxicity of a variety of synthetic progestins. Animal data indicate that most of these progestins have little or no teratogenic potential but may have embryolethal effects depending upon the dosage, the time, and the duration of treatment. Here we will consider only those studies in which fetal exposure included the period of organogenesis (Table 4).

In nonhuman primate studies no teratogenic effects were observed in rhesus monkeys after administering HPC during early organogenesis (Courtney and Valerio, '68). Wharton and Scott ('64) administered norethindrone to pregnant rhesus monkeys from the fourth week of gestation to term and observed an increase in stillbirths, virilization of female infants, and cryptorchidism in male infants; no effects were observed in the nongenital organs. Prahalada et al. ('85a,b) observed malformations of the external genitalia in infants of both sexes and a reduction in weight of the adrenal gland in both cynomolgus macaques and baboons with either single or multiple doses of medroxyprogesterone acetate (MPA).

Table 4 summarizes the findings from additional studies in laboratory animals with synthetic progestins. The results of these investigations can be placed into three categories: 1) no embryotoxic effects (Morrissette et al., '64; Peterson and Edgren, '65; Jung and Peters, '67; Andrew and Staples, '77; Bruce and Bartholomeusz, '76), 2) some degree of embryolethality with no other adverse effects observed (Roy and Kar, '67; Overbeek et al., '62; Neuweiler and Richter, '64; Saunders and Elton, '67; Seegmiller et al., '83), and 3) a low incidence of embryo or fetal death, malformations, and/or growth retardation at highest doses administered (Takano et al., '66; Gidley et al., '70; Eibs et al., '82; Andrew and Staples, '77).

The literature on embryotoxicity studies using estrogens (natural and synthetic) and progesterone in lab animals is too extensive and diverse to adequately summarize here. However, it appears that for most of these compounds embryo or fetal death in the absence of significant teratogenicity was the primary embryotoxic effect observed (Greene et al., '40; Friere, '55; Nishihara, '58; McLean-Morris and Van Wagenen, '66, '73; Saunders and Elton, '67; Jung and Peters, '67; Kennelly, '69; Haddad and Ketchel, '69; Jean and Jean, '70; Gabriel-Robez et al., '72; Ornoy, '73; Bartholomeusz and Bruce, '76; Coyle et al., '76).

In the present study, unlike most other teratogenicity studies conducted in nonhuman primates, administration of the drugs was continued throughout the pregnancy in an attempt to simulate the conditions in humans for maintenance of pregnancy. Only a very low incidence of nonspecific structural changes were detected in either species for either drug in those fetuses which survived until teratogenic evaluation at term. Such negative findings in nonhuman primates support previous animal data which failed to show a correlation between in utero sex steroid exposure and genital or nongenital teratogenicity.

Concern regarding the association between treatment with long-acting hormones during pregnancy and developmental toxicity has been the subject of several recent reviews in the literature on humans. Schardein ('80), Wilson and Brent ('81), Wiseman and Dodds-Smith ('84), Katz et al. ('85), and Resseguie et al. ('85) have concluded from retrospective or prospective epidemiologic studies that female sex hormones do not present a relevant teratogenic risk. The results of the present study, in agreement with animal and human data, indicate that HPC used alone or in combination with estrogen has no significant teratogenic potential.

TABLE 4. Summary of laboratory animal studies on commonly used synthetic progestins[1]

Compound	Species	Daily dosage/ route	HDE	Days	Embryotoxicity	Reference
Norethindrone	Rhesus monkeys	25 mg, i.m.	42×	27–term	Embryolethality, genital defects	Wharton and Scott ('64)
Hydroxyprogesterone caproate	Mice (ARS Swiss Webster)	42, 416, and 833 mg/kg, s.c.	10, 100, and 200×	6–15	Embryo- and maternal lethality	Seegmiller et al. ('83)
	Wistar rats	0.05 mg, i.m.	0.06×	12–21	No embryotoxicity	Jung and Peters ('67)
	Rhesus monkeys	125 mg, p.o.	4.5×	Variable	No embryotoxicity	Courtney and Valerio ('68)
Medroxyprogesterone acetate	NMRI mice	30 mg/kg, s.c.	12×	1–12 (single day)	Embryolethality, growth regardation, and nongenital defects	Eibs et al. ('82)
	CD1 and AJ mice, CD rats	3–3,000 mg/ kg, s.c.	1.2–1,200×	7–15 (3,6, or 9 days)	No embryotoxicity	Andrew and Staples ('77)
	New Zealand and Dutch-belted rabbits	0.1-30 mg/ kg, s.c.	0.04–12×	8–16 (3,6, or 9 days)	Embryolethality, growth retardation and cleft palate	Andrew and Staples ('77)
	Wistar rats	1 mg, i.m.	2×	7	No embryotoxicity	Bruce and Barthlomeusz ('76)
	New Zealand white rabbits	5 mg, i.m.	0.6×	6	No embryotoxicity	
	Cynomologus macaque	2.5–100 mg/kg, i.m.	10–40×	27 ± 2 (single day)	Genital and adrenal defects	Prahalada et al. (85a)
	Baboon	2.5–100 mg/kg, i.m.	1–40×	27 ± 2 (single day)	Genital and adrenal defects	Prahalada et al (85b)
Norethynodrel and metabolites	CF1 mice	0.15–0.6 mg/kg, p.o.	1.5–5.8×	8–10 or 11–13	Embryolethality, genital and non-genital defects	Gidley et al. ('70)
Norethynodrel	Charles River rats	0.01–0.1 mg, p.o.	0.3–3×	−5 to term (35 days)	No embryotoxicity	Peterson and Edgren ('65)
	Rats	0.0083–2.5 mg/kg, s.c.	0.1–30×	10–17	Embryolethality, genital defects	Roy and Kar ('67)

Chlormadinone acetate	Japanese dds and CF1 mice	1–50 mg/kg, p.o.	20–1,000×	8–17 (variable)	Embryolethality, cleft palate	Takano et al. ('66)
	Japanese albino rabbits	1–10 mg/kg, p.o.	20–200×	8–20	Embryolethality, nongenital defects	Takano et al. ('66)
Cyproterone acetate	NMRI mice	30 mg/kg, s.c.	—	1–12 (single day)	Growth retardation, nongenital defects	Eibs et al.('82)
Norethandrolone	Rats (4 strains)	0.5–5.0 mg/kg, i.m.	—	8–15	Embryolethality	Neuweiler and Richter ('64)
Ethynodiol diacetate	Dutch-belted rabbits	0.01–2.0 mg/kg, p.o. or s.c.	0.4–80×	0 or 10 to 28	Embryolethality, no teratogenicity	Saunders and Elton ('67)
17-acetoxyprogesterone	Holtzman rats	5–30 mg/kg, p.o.	—	1–13	No embryotoxicity	Morrissette et al. ('64)
Lynestrenol	Rats	2.5–10 mg, p.o.	100–400×	9–20	Embryolethality, no teratogenicity	Overbeek et al. ('62)

[1]Unless stated otherwise in the cited reference, HDEs are based on estimated human contraceptive doses and a mean female body weight of 60 kg. p.o. = per os (oral); s.c. = subcutaneous; i.p. = intraperitoneal; i.m. = intramuscular.

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