1. Chemical and Physical Data

1.1 Synonyms and trade names*

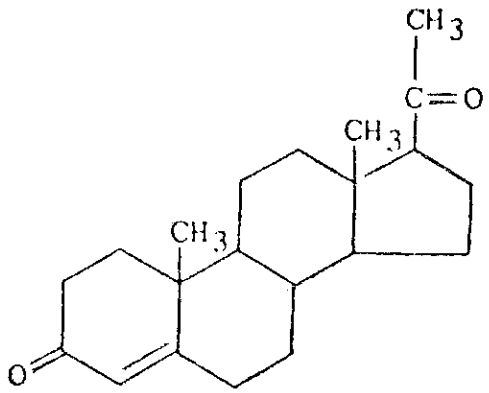
Chem. Abstr. No.: 57-83-0

Corpus luteum hormone; luteal hormone; luteohormone; luteine; pregn-4-en-3,20-dione; 3,20-pregnene-4; pregnenedione; pregnene-3, 20-dione; pregn-4-ene-3,20-dione; Δ^4-pregnene-3,20-dione; 4-pregnene-3,20-dione; β-progesterone; progesteronum; progestin

Corlutin; Corlutina; Corluvite; Corporin; Cycloestrol; Duogynon; Emmenovis; Emonovister; Farlutal; Flavolutan; Foliluteina; Fologenon; Gestone; Gestormone; Glanducorpin; Hormoflaveine; Hormoluton; Lipo-lutin; Lucorteum sol; Luteinique; Luteocrin; Luteodyn; Luteo Folicular; Luteogan; Luteogyl; Luteol; Luteosan; Luteostab; Luteovis; Lutestex; Lutestron; Lutex; Lutidon; Lutocycli Lutocyclin M; Lutocylin; Lutoform; Lutogyl; Lutovitamina E; Lut Ovociclina; Lut-ovocyclin; Lutren; Lutrogen; Lutromone; Lutrone; Nalutron; Percutacrine Lut.; Piaponon; Precyclan-Leo; Primolut; Progekan; Progesterol; Progesterone R; Progestilline Fort; Progestogel; Progestone; Prolidon; Proluton; Proluton D; Proluton Dep.; Proluton-Oestradiol; Proluton Z; Protectona; Stroluten; Synergon; Syngesterone; Synovex S; Syntoluton; Testo Luteinica; Testoluton; Testoviron Prog.; Tocogestan; Trioestrine; Trioestrine R; Trioestrine Vitam.; Vit-E-Progesterone

* Trade names include mixtures containing progesterone

1.2 Chemical formula and molecular weight



$C_{21}H_{30}O_2$

Mol. wt: 314.5

1.3 Chemical and physical properties of the pure substance

(a) Description: Exists in two readily interconvertible forms:-

α-form - white orthorhombic crystals

β-form - white orthorhombic needles

(b) Melting-point: α-form - 127-131°C

β-form - 121°C

(c) Absorption spectrometry: λ_{max} 240 nm

(d) Optical rotation: $\{\alpha\}_D^{20}$ +172° to +182° (2% w/v in dioxane)

(e) Solubility: Practically insoluble in water; soluble at 25°C in 95% ethanol (1 in 8), arachis oil (1 in 60), chloroform (1 in 0.33), ether (1 in 16), ethyl acetate (1 in 60), light petroleum (1 in 100); also soluble in acetone, benzene, dioxane and oils

1.4 Technical products and impurities

Progesterone is available in the United States in the form of injections, as an aqueous suspension and as a solution in vegetable oil. Combinations of progesterone and oestrogenic substance are also available, in the form of tablets and of injections of aqueous suspensions and oil solutions (Kastrup, 1973).

2. Production, Use, Occurrence and Analysis

2.1 Production and use[1]

Isolation of progesterone was first reported by Butenandt & Westphal (1934) and by Wintersteiner & Allen (1934); numerous methods of synthesis from other steroids (e.g., cholesterol and stigmasterol) were subsequently reported. One of the two US manufacturers of progesterone is believed to produce it from intermediates obtained by the degradation of diosgenin. In one method, degradation produces pregnenolone, which is converted to progesterone by Oppenauer oxidation. The other US manufacturer of progesterone is believed to produce it from intermediates derived from stigmasterol.

Until about 1944 world production of progesterone was only a few kg per year, and even in 1951 it was less than 1 000 kg. However, in 1952 one Mexican manufacturer alone produced over 9 000 kg (Anon., 1967). The present annual production of the two US manufacturers is not known.

In the past progesterone was recommended for use in the treatment of a large number of menstrual disorders, e.g., abnormal uterine bleeding due to hormonal imbalance, ammenorrhea, habitual abortion and threatened abortion. However, in some of these applications it has been displaced by orally active progestins, and its efficacy in other uses has been put into question. In October 1973 the US Food and Drug Administration proposed to restrict the approved uses of progesterone injection to the treatment of amenorrhea and of abnormal uterine bleeding due to hormonal imbalance, in the absence of organic pathology such as submucous fibroids or uterine cancer (US Environmental Protection Agency, 1973). Combinations of progesterone with oestrogenic substances (as injections or tablets) are used for the treatment of secondary amenorrhea or of functional uterine bleeding (Kastrup, 1973). Prior to the recent governmental action, total US sales of progesterone for use in human medicine were estimated to have been less than 50 kg annually.

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[1] Data from Chemical Information Services, Stanford Research Institute, USA

Data on production of progesterone in the countries of Western Europe are not available, but it is believed that one company in France manufactures the chemical. Total sales of progesterone in hormone specialties in Western Europe in 1972 are estimated to have been less than 500 kg. Sales in France represented approximately 60% of the total, with lesser amounts sold in Belgium, the Federal Republic of Germany, Italy, The Netherlands and Spain.

Subcutaneous ear implants of combinations of progesterone and oestradiol benzoate are approved in the US for the promotion of growth and feed efficiency in lambs and steers (US Code of Federal Regulations, 1973), and the quantity of progesterone used for this purpose may have increased in recent months as a result of the US Food and Drug Administration ban on the use of diethylstilboestrol implants as a growth promoter for these animals.

Veterinary uses of progesterone include control of habitual abortion in cattle and delay of oestrus and ovulation in cattle, pigs and dogs (Merck & Co., 1968). No data are available on the quantity of progesterone consumed in the US for veterinary purposes.

2.2 Occurrence

Progesterone is a widely-occurring, natural progestin (see section, "General Remarks on the Sex Hormones", p. 30, for further information).

2.3 Analysis

General methods of analysis are summarized in the section, "General Remarks on the Sex Hormones", p. 40.

3. Biological Data Relevant to the Evaluation of Carcinogenic Risk of Man

3.1 Carcinogenicity and related studies in animals

(a) Subcutaneous and/or intramuscular injection

Mouse: Burrows & Hoch-Ligeti (1946) found that up to 34 weekly s.c. injections of 1 mg progesterone in arachis oil did not increase the incidence of breast tumours in 30 female C3H mice compared with that in 20

controls; however, the incidence was very high in both the treated and control groups, and tumours occurred at an early age. {This may have obscured any effect, and the age at the start of treatment was also quite advanced. Similar reservations apply to the results of Heiman (1945), who used RIII mice.}

Jull.(1954) found that s.c. administration of 0.5 µg progesterone every two weeks combined with 50 µg oestradiol dipropionate in oil given once a week to ovariectomized IF mice increased the incidence of tumours induced by 3-methylcholanthrene compared to that produced by oestrogen only plus the carcinogen (the respective incidences were 9/11 and 2/20). Similar but less significant results were found in male mice, the incidences being 4/14 and 1/29.

Kaslaris & Jull (1962) found that 10 mg progesterone injected s.c. in arachis oil weekly until death reduced the induction of adenocarcinomas in the uterine horns of mature ovariectomized CBA mice exposed to local implants of 0.1 mg 3-methylcholanthrene from 23 to 0%; however, there was a corresponding increase from 3 to 31% in the incidence of connective tissue tumours.

Poel (1965) found that 2.5 mg progesterone in peanut oil given s.c. 5 times weekly for 19 weeks increased the incidence of breast tumours induced by 3-methylcholanthrene (MCA) in C3H female mice (with the MTV) to 23/23, compared with 5/24 for MCA alone and 2/25 for progesterone alone. A similar action of progesterone with MCA was observed in groups of 26-28 C3H mice without the MTV, although the effect in this case was mainly to shorten the latent period from 40 to 25 weeks. When progesterone alone was administered to C3H mice with the MTV the incidence of breast tumours was increased from 6/24 with vehicle only to 21/24, and the latent period was diminished from 70 to 55 weeks. Progesterone alone given to 27 C3H mice without the MTV did not induce tumours within 42 weeks (Poel, 1968; 1969).

Glucksmann & Cherry (1962) reported that the incidence of mixed carcinomas of the cervix or vagina in female C3H mice given weekly intravaginal applications of a 1% solution of 9,10-dimethyl-1,2-benzanthracene (DMBA) was increased by ovariectomy. The incidence of mixed carcinomas in ovariectomized,

DMBA-treated mice was 3/8 (38%), compared with 0/17 in intact, DMBA-treated mice; and squamous-cell carcinomas of the cervix or vagina occurred in 5/15 ovariectomized mice, compared with 13/17 (76%) intact mice. In a group of 16 ovariectomized C3H females given the DMBA treatment together with twice-weekly i.m. injections of 0.2 mg progesterone, the incidence of squamous-cell carcinomas reached 13/16 (81%), and mixed carcinomas occurred in 5/16 (31%) mice.

Rat: In rats, progesterone injected s.c. or i.m. at doses of 3-4 mg/day decreased the latent period and/or increased the incidence of breast tumours induced by single doses of 20 mg DMBA or of 10 mg MCA, but only when injections were commenced after administration of the carcinogen (Huggins et al., 1959; Huggins & Yang, 1962; Jabara et al., 1973). In other experiments, where progesterone was injected for varying periods before administration of a carcinogen, the resulting incidence of breast tumours was significantly diminished from 13/20 to 6/16 (Jull, 1966; Briziarelli, 1966; Welsch et al., 1968; Jabara et al., 1973). Other experiments, in which progesterone was injected s.c. together with an oestrogen after dosage with DMBA, are difficult to interpret due to the known inhibitory effects of oestrogens on mammary carcinogenesis (McCormick & Moon, 1973). It has been shown that oestrogen treatment of ovariectomized female rats is not sufficient to restore susceptibility to mammary carcinogenesis by MCA; however, treatment with a combination of progesterone with oestrogen i.m. is a sufficient replacement for the ovaries (Sydnor & Cockrell, 1963). Cantarow et al. (1948) reported an increase from 17/57 to 22/26 in the incidence of breast tumours in female rats fed 0.03% 2-acetylaminofluorene in the diet and injected i.m. with 0.5 mg progesterone 3 times weekly for life.

Progesterone (0.3 mg) injected s.c. 3 times weekly for 21 weeks increased the latent period of induction of breast tumours in female hooded rats by oestrone from 37 to 50 weeks but did not change the incidence of mammary tumours (Cutts, 1964).

In intact rats, i.m. injections of progesterone (1 mg twice weekly) retarded by approximately 4 weeks the induction of sarcomas of the cervix

and vagina produced by local application of 1% DMBA in acetone weekly for life, but the induction of papillomas was promoted by 19 weeks. Progesterone alone did not increase the rate of carcinogenesis in ovariectomized rats treated with the carcinogen; however, when it was combined with oestrogen, the incidence but not the latent period of tumour induction was restored to that of intact females (Glucksman & Cherry, 1968).

Rabbit: 10 mg progesterone injected s.c. twice weekly into 32 rabbits exposed to vaginal strings containing 3-methylcholanthrene did not affect the incidence of vaginal tumours occurring within 20 months, the incidences being 5/23 in controls compared with 4/31 in treated animals (Alvizouri & Ramiréz de Pita, 1964).

Dog: Long-term s.c. injections of progesterone for a total of 74 weeks, increasing in dosage from 0.08 to 22.5 mg daily, caused endometrial hyperplasia, inhibition of ovarian development and marked mammary hyperplasia in female beagle dogs. No tumours were reported in animals killed 24 hours after the last dose, but fibro-adenomatous nodules occurred in 2/5 dogs given the highest doses of progesterone (Capel-Edwards et al., 1973).

(b) Subcutaneous implantation

Mouse: Trentin (1954) implanted high doses of progesterone (14 mg pellets every 28 days during 104 weeks) s.c. in 59 female C3H x A hybrid mice (with the MTV) and found breast carcinomas at a significantly earlier age and in a higher incidence (88% at 70 weeks) than among 58 untreated control mice (62% at 93 weeks). No mammary tumours appeared among 27 intact or among 24 castrated, untreated, male controls or in 27 progesterone-treated, intact males. However, 2/26 castrated males given progesterone developed mammary tumours.

Lipschütz et al. (1967a) found that the absorption of 29 µg/day or more of progesterone from pellets implanted s.c. was required to suppress corpus luteum formation in the ovaries of mice. After 18 months' treatment with 59-900 µg/day progesterone, so-called ovarian granulosa-cell tumours were found in 27/83 BALB/c mice. Only 3 of these tumours exceeded 5 mm in size, most of them measuring less than 0.5 mm in diameter. One microscopic

tumour occurred among 33 control mice killed after 18 months.

Following the absorption from s.c. pellets of 18-900 µg/day progesterone alone, uterine sarcomas were observed in 15/142 mice after a period of 18 months. Most of these tumours were very small, and no tumours were found in 33 controls (Lipschütz et al., 1967b).

A group of 20 female BALB/c mice treated with 5 mg s.c. pellets of a progesterone-cholesterol mixture for an average period of 17 months developed no precancerous or cancerous lesions of the cervix and/or vagina. However, when 39 mice were treated with intravaginal inoculations of herpesvirus type 2 in addition to the progesterone pellets, 1 precancerous lesion and 1 squamous-cell carcinoma of the cervix were observed. No tumours of the cervix or vagina were found in 15 control mice (Muñoz, 1973).

After local applications of the carcinogen 3-methylcholanthrene (MCA) in 50 C57BL6 mice, Reboud & Pageaut (1973) found that 15 mg progesterone implanted s.c. every 3 weeks for 9 weeks increased the incidence of vaginal-cervical invasive squamous-cell carcinomas from 6/50 with MCA alone to 45/50.

Rat: In A x C rats implanted s.c. with 25 mg pellets containing 20 mg progesterone/100 g bw and observed for 40 weeks, an increased incidence of liver-cell carcinomas induced by N-2-fluorenyldiacetamide was observed in intact male rats (11/11 versus 7/12), in castrated males (5/13 versus 1/9) and in ovariectomized females (4/12 versus 0/14), but the treatment did not increase the incidence of these tumours in intact females (0/9 versus 1/10) (Reuber & Firminger, 1962).

In female A x C rats treated with diethylstilboestrol (DES) and/or progesterone (20 mg implanted intrascapularly) plus irradiation, the development of mammary tumours was inhibited in the presence of progesterone. The incidence was reduced from 12/21 with DES + irradiation to 1/21 with DES + progesterone + irradiation; the incidence was 0/11 with progesterone + irradiation (Segaloff, 1973).

3.2 Other relevant biological data

See section, "General Remarks on the Sex Hormones", and pp. 38-40.

3.3 Observations in man

See section, "Oestrogens and Progestins in Relation to Human Cancer", p. 219.

4. Comments on Data Reported and Evaluation[1]

4.1 Animal data

Progesterone was tested by subcutaneous or intramuscular injection in mice, rats, rabbits and dogs and by subcutaneous implantation in mice and rats. It was tested alone only in mice and dogs; in rats and rabbits it was always given in combination with other chemicals; in mice it was also tested in combination with other carcinogens.

When given alone, it increased the incidence of ovarian, uterine or mammary tumours in mice, while the experiment in dogs was of insufficient duration to allow an assessment to be made.

The administration of progesterone to intact or castrated mice and rats and to rabbits in combination with polycyclic aromatic hydrocarbons or with 2-acetylaminofluorene and/or oestrogen variously affected the incidence and the histological type of the tumours produced by these known carcinogens (mainly mammary, uterine and vaginal tumours). In particular, progesterone enhanced the incidence of tumours produced by these known carcinogens, but only when given after and not before their administration.

4.2 Human data

No case reports or epidemiological studies on progesterone were available to the Working Group.

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[1] This section should be read in conjunction with the section "General Conclusions on Hormones", p. 235.

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