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PROCESS OF ESTABLISHING CYCLICITY IN A HUMAN FEMALE

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U.S. Cl. 424—242 1 Claim

ABSTRACT OF THE DISCLOSURE

Improved methods of systemically administering estrogens to human females wherein the estrogen is administered sequentially in gradually increasing amounts over a predetermined span of time. The estrogen administration is advantageously supplemented with concomitant systemic administration of a progestogen. Beneficial results are achieved in contraceptive regimens and in menopausal and perimenopausal regimens.

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a continuation-in-part of Ser. No. 519,412 filed Jan. 10, 1966 now abandoned, which in turn is a continuation-in-part of Ser. No. 351,857, filed Mar. 13, 1964, now abandoned.

BRIEF SUMMARY OF THE INVENTION

This invention relates to a process which is useful in medical applications, more particularly an improved process of systemically administering estrogen to females wherein the estrogen is sequentially administered in graduated amounts in accordance with a predetermined dosage regimen. It also relates to an improved process of graduated sequential administration of estrogen which includes concomitant systemic administration of predetermined dosages of progestogen.

DESCRIPTION OF PREFERRED EMBODIMENTS

As used herein the term estrogen means naturally occurring and synthetic substances capable of evoking typical changes in the accessory sex organs of the female subjects, namely thickening of vaginal mucosa, hypertrophy of the myometrium and proliferation of the endometrium. Such substances are, for example, estriol, estrone, estradiol, estradiol cyclopentylpropionate (estradiol cypionate), estradiol, dipropionate, estrogenic substances conjugated, ethinyl estradiol, ethinyl estradiol 3-methyl ether, piperazine estrone sulfate, benzesterol, dienesteriol, diethylstilbesterol, diethylstilbesterol dipropionate, hexesterol, methallenestril, and the like. Of these substances, ethinyl estradiol is preferred. As is known in medical applications, the said and equivalent estrogens have attained acceptance as useful additions to the constantly enlarging armamentarium of medicinal agents. Clinical areas wherein estrogenic regimens are useful include the menopause, of natural origin and that due to surgical or other intervention; ovarian agenesis, a condition in which normal cycling does not occur; primary dysmenorrhea, dysfunctional bleeding and oligomenorrhea. The dosages of estrogen heretofore administered for

the treatment of the above clinical conditions are properly designated as palliative dosages following which regression of the endometrial tissue occurs in the absence of bleeding. Such treatment differs markedly from the herein described graduated sequential administration of the estrogen, which provides a more normal cyclic surge of active ingredient and a full blown endometrial response.

Although the herein described invention is more specifically related to graduated sequential administration of estrogen in accordance with a predetermined dosage regimen, such regimen is also useful in combination with dosages of a progestogen. In both artificial and natural menopause such added progestogen prevents the development of a proliferative-type hyperlasia. This is also true of the clinical ovarian agenesis condition. Moreover, in regularly cycling females the graduated sequential estrogen treatment of the present invention plus an added progestogen finds medical application because of inhibition of ovulation, or action of other contraceptive factors, Additionally, in dysfunctional bleeding, oligomenorrhea, and primary dysmenorrhea, the combined dosage regimen provides regular cycles in the female subjects, rather than cycles of a highly irregular type. These subjects are in need of cyclicity for the physiological and psychological benefits provided in these clinical conditions.

As used herein the term progestogen means those substances of natural and synthetic origin which are capable of inducing secretory changes of the endometrium, simulating growth of the mammary alveolar tissue, and relaxing the uterine smooth muscle. Such substances are, for example, duphastone, dimethisterone, chlormadinone, hydroxyprogesterone caproate, medroxyprogesterone acetate, norethindrone, norethynodrel, progesterone, melengestrol acetate and the like. Of these substances medroxyprogesterone acetate is preferred.

It has been found in accordance with the present process of predetermined administration of estrogen that distinct advantages and differences exist in comparison with the heretofore utilized process of administering estrogen. For example in the area of gastrointestinal tolerance, less nausea is encountered. In the area of breast problems, less breast tenderness is encountered. Moreover, the present process provides constant estrogen coverage with accompanying salutary effects on the integrity of the vascular endothelium, due to beneficial effects on serum lipid levels. Other unexpected advantages obtained in carrying out the present process include less breakthrough bleeding and absence of amenorrheic cycles. Consequently, there is provided in accordance with the present invention an improvement in the systemic administration of estrogen to females which consists essentially of sequentially administering the estrogen in graduated amounts, that is, in increments with the second dosage being larger than the first and the third dosage being larger than the second. Although the amount of the first dosage varies with the particular estrogen, the second and third dosages thereof are in ascending order. Such dosages in increments advantageously ready the uterine tissue, by thickening and growth, for the secretory phase incidental to any desired concomitant administration of a final estrogen-progestogen dosage as heretofore described.

The beginning dosage of the estrogen is that usually referred to as a reparative dosage for the endometrium. The first and second increments are maintenance and ripening dosages respectively. These dosages vary with the potency of the individual agents and their preferred route of administration.

Approximate milligram dosages of representative estrogens are as follows:

Oral estrogen	Dosage (mg.)		
	Reparative	Maintenance	Ripening
Ethinyl estradiol	0.025 to 0.05	0.075 to 0.1	0.125 to 0.15.
Conjugated estrogen	1.25	2.5	3.75.
Piperazine estrone sulfate	1	2	3.
Dienestrol	1	2	3.
Diethylstilbesterol	1	2	3.
Hexestrol	3	6	9.
Methallenestril	3	6	9.
Estradiol cyclopentylpropionate	2.5	5	10.
Estradiol valerate	2.5	5	10.
Range	About 0.025 to 3	About 0.075 to 6	About 0.125 to 10.

Illustrative dosages in milligrams of representative progestogens which can be used in a combination dosage regimen are as follows:

Medroxyprogesterone acetate: 10 mg. orally
Norethindrone: 20 mg. orally
Norethynodrel: 20 mg. orally
Medroxyprogesterone acetate: 35 mg. intramuscularly
Hydroxyprogesterone caproate: 250 mg. intramuscularly
Melengestrol acetate: 5 mg. orally 15 mg. intramuscularly
Range: About 5 to 250

Operable dosages of other active ingredients are determined in reference to the age, weight and condition of the female subject under treatment, always maintaining the above-stated relationships of estrogen dosage, namely reparative, maintenance and ripening amounts, and the secretory amount of the progestogen whenever a concomitant administration process is utilized. It is preferred to utilize estrogen of small particle size, e.g., 75% of particles being smaller than about 10 microns and 99% smaller than about 20 microns. Similarly the progestogen is reduced in particle size. Such reduction is particle size provides advantageously higher physiologic levels of active ingredients.

The present process consists essentially of treating the subject females with predetermined dosages of estrogen in two increments in a predetermined dosage regimen spanning 28 to 32 days. When oral estrogen is used, the medical application is preferably provided by daily dosages to supply the subjects with the aforesaid reparative, maintenance and ripening amounts for a predetermined number of days. When parenteral, that is long-acting or repository, estrogen is used, treatment is spaced to provide said amounts for the predetermined number of days. The days on which the increments on parenteral materials are injected need not coincide with the days on which the increments of oral material are administered. However, the increased supply of active ingredients available to the subject will substantially coincide in point of time. Likewise, in the case of concomitant oral administration of progestogen, it is preferably administered daily, whereas with a repository product, one dosage can provide the secretory amount for the predetermined number of days. Generally, the active medicaments are supplied to the subject females over the prescribed regimen or space of time; supply being daily when oral, and when parenteral at intervals designed to supply the effective amount during the space of days. The present process provides cyclicity wherein regular build-up and break-down of the uterine endometrium comprises a post-menstrual phase, an interval phase, a secretory phase, and menstruation, such build-ups and break-downs spanning, as aforesaid, a predetermined time period of from about 28 to about 32 days. It is over this time period that the dosage regimen is followed, preferably for about 28 days.

An interval of 7 to 10 days between repeated dosage regimens is operable. However, in the case of progestogen-supplemented regimens, especially contraceptive regimens, such intervals are occasional only and are usually omitted. The subjects to be treated are, of course, non-

gravid. As aforesaid, the amounts of the respective active ingredients, frequency and routes of administration, oral, parenteral or local, for example intravaginal, are determined in reference to the relative potencies, duration of response for a given dosage, and the most advantageous route of administration. Oral administration is preferred; however such administration can be coupled with parenteral administration. Also, oral administration can precede the parenteral and the order of precedence can be reversed. Intravaginal and intrauterine administration, can be used in the aforesaid dosage regimens, although not preferred. Depending upon the route or administration, the active substances can be suitably administered with various diluents, excipients, binding and disintergrating agents, antimicrobial agents, sterile vehicles and the like in the form of tablets, capsules, sterile suspensions, and similar dosage forms.

The following examples set forth how to perform the novel process and the best mode contemplated of carrying out the invention but are not to be construed as limiting.

EXAMPLE 1

Graduated sequential oral administration of estrogen

Menopausal patients are provided sustained support by the following dosage regimen spanning 28 days:

Days 1 through 7: Daily oral dosage of 0.05 mg. of ethinyl estradiol
Days 8 through 21: Daily dosage of 0.1 mg. of ethinyl estradiol
Days 22 through 28: Daily dosage of 0.15 mg. of ethinyl estradiol

Especially beneficial results are obtained in lessened gastrointestinal upsets. This dosage regimen is also advantageously beneficial in establishing regular cyclicity in otherwise irregularly cyclic nongravid female subjects.

EXAMPLE 2

Graduated sequential oral administration

Post-menopausal patients obtain especially beneficial results in freedom from psychosomatic complaints such as anxiety, fatigue, and lack of mental alertness.

Days 1 through 7: Daily oral dosage of 1 mg. diethylstilbesterol
Days 8 through 21: Daily oral dosage of 2 mg. diethylstilbesterol
Days 22 through 28: Daily oral dosage of 3 mg. diethylstilbesterol

EXAMPLE 3

Graduated sequential parenteral administration

Ovariectomized subjects are treated in accordance with the following cyclic dosage regimen. Especially beneficial results are obtained in regularity of cyclicity and freedom from mental and physical discomfort.

Day 1: 2.5 mg. estradiol cyclopentylpropionate, intramuscularly
Day 8: 5 mg. estradiol cyclopentylpropionate, intramuscularly

Day 15: 10 mg. estradiol cyclopentylpropionate, intramuscularly

EXAMPLE 4

Progestogen supplemented regimen

Menopausal patients are treated in accordance with the oral dosage regimen of Example 1 through Days 1 through 7 and Days 8 through 21, with dosage on Days 22 through 28 of 10 mg. orally of medroxyprogesterone acetate in addition to the 0.15 mg. of ethinyl estradiol. A proliferated-type hyperplasia is inhibited; meanwhile the advantages associated with the graduated sequential estrogenic therapy are nonetheless obtained.

Such combined dosage regimen provides infertile cycles in regularly cycling females otherwise normally fertile.

EXAMPLE 5

Progestogen supplemented regimen

The regimen of Example 2 in the medical applications to post-menopausal patients is followed in accordance with Days 1 through 7 and Days 8 through 21; however during the period of Days 22 through 28, a daily oral dosage of 20 mg. of norethindrone is supplied. As in Example 2, the patients obtain especial beneficial results in freedom from psychosomatic complaints such as anxiety, fatigue, and lack of mental alertness.

EXAMPLE 6

Progestogen supplemented regimens

Likewise, supplemental regimens are advantageously beneficial in providing essentially normal cycles in cases of primary dysmenorrhea, dysfunctional bleeding and oligomenorrhea.

EXAMPLE 7

Otherwise normally fertile human females are treated in accordance with the following dosage regimen which provides infertile cyclicity: Days 1 through 7, daily oral dosage of 0.025 mg. of ethinyl estradiol; days 8 through 21, daily oral dosage of 0.1 mg. of ethinyl estradiol; days 22 through 28, daily oral dosage of 0.125 mg. of ethinyl estradiol and 10 mg. of medroxyprogesterone acetate.

EXAMPLE 8

Contraceptive regimen

The daily dosages are given in accordance with the following systemic administration regimen: Days 1 through 7, a daily intravaginal dosage of a reparative amount of estrogen; days 8 through 21, a daily intravaginal dosage of a maintenance amount of estrogen; days 22 through 28 a daily intravaginal dosage of a ripening amount of estrogen and a secretory amount of progestogen. Equally beneficial infertile cycles are obtained in this dosage regimen.

EXAMPLE 9

The following intravaginal dosage regimen is administered to otherwise fertile human females and infertile cycles result. Days 1 through 7, a daily intravaginal dose of 0.5 mg. of estradiol cypionate; days 8 through 21, a daily intravaginal dosage of 1 mg. of estradiol cypionate; days 22 through 28 a daily intravaginal dosage of 1 mg. of estradiol cypionate and 10 mg. of medroxyprogesterone acetate.

What is claimed is:

1. A process of establishing cyclicity in a human female which consists essentially of providing to said female estrogen and progestogen orally in accordance with the following predetermined dosage regimen: For about 7 days a daily dosage of about 0.025 milligram of ethinyl estradiol, for the succeeding about 15 days a daily dosage of about 0.1 milligram of ethinyl estradiol and for the succeeding about 7 days a daily dosage of about 0.125 milligram of ethinyl estradiol and about 10 milligrams of medroxyprogesterone acetate.

References Cited

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