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3,814,809

SUSTAINED RELEASE CONTRACEPTIVE COMPOSITION AND METHOD OF USE

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No Drawing. Filed Nov. 11, 1971, Ser. No. 197,959

Int. Cl. A61j 3/00, 3/08; A61k 27/00

U.S. Cl. 424-19

15 Claims

ABSTRACT OF THE DISCLOSURE

Compositions comprising prostaglandin $F_{2\alpha}$ or E_2 , oxytocin, and copper or zinc salts of ethylene diamine tetraacetic acid with a portion of the prostaglandin being dissolved in a biodegradable wax; in the form of vaginal suppositories and/or impregnated tampons and methods of preventing conception or implantation by vaginal insertion of said compositions after exposure to conception are useful contraceptive aids in mammals.

BACKGROUND OF THE INVENTION

1. Field of the invention

The compositions of the instant invention are useful as contraceptive aids in mammals.

2. Description of the prior art

A. S. M. M. Karim et al. [British Medical Journal, 4, 621-623 (1968)] report the use of prostaglandin $F_{2\alpha}$ in fusion in the induction of labor.

B. B. B. Pharriss [Science News, 95, 65-66 (1969)] reports the use of prostaglandin $F_{2\alpha}$ in the prevention of conception.

C. V. R. Pickles [International Journal of Fertility, 12, 335-338 (1967)] reports prostaglandin $F_{2\alpha}$ as the most potent of the prostaglandins in stimulating the human myometrium.

D. The Lancet, May 2, 1970 (pp. 927-928), reports the use of prostaglandins in the induction of labor or abortion.

E. The Lancet, January 31, 1970 (pp. 223-226) contains a treatise on prostaglandins, including their use and chemistry.

The use of systemic prostaglandins as abortifacients has been reported in man [Karim and others, Lancet I, 1115 (1970)], and their local use has been suggested. However, compositions with combined luteolytic and antizygotic properties have not been suggested. This invention is considered novel in the sustained release form of the prostaglandin, together with the use of copper or zinc salts of ethylene diamine tetraacetic acid as gametocidal agents, and in the use of oxytocin to improve tubal transport.

Furthermore, R. Ravenholt, Director of the U.S. Office of Population of the Agency for International Development has indicated (Drug Research Reports, July 21, 1971) that manufacturers should be interested in developing a special prostaglandin releasing tampon.

Contraceptive compositions are disclosed, as well as methods for preventing conception or implantation, using as dosage forms (a) a vaginal suppository and/or (b) impregnated hydrophilic polyurethane or cellulose tampons as drug delivery vehicles. The active ingredients are designed to operate at different points in the reproductive mechanism to permit more latitude in the operation of the system. The active ingredients are specifically prostaglandin $F_{2\alpha}$ or E_2 plus oxytocin in a sustained release vehicle to exert a luteolytic effect without having to rely entirely on tissue diffusion, and zinc or copper salts of disodium ethylene diamine tetraacetic acid to produce an antizygotic effect. Oxytocin improves tubal transport of the active ingredients in a physiological manner.

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Preferably the compositions will contain, per dosage form, from about 100 μ g. to about 10 mg. of prostaglandin $F_{2\alpha}$ or E_2 , from about 1 μ g. to about 1000 μ g. of oxytocine, from about 10 mg. to about 1000 mg. of copper or zinc salt of ethylene diamine tetraacetic acid.

COMPLETE DISCLOSURE

It has long been an object of the pharmaceutical industry to discover a safe and effective method of either preventing conception or terminating a conception in the very early stages of the "pregnancy."

The object has been achieved by the formulation of the composition of the present invention which comprises prostaglandin $F_{2\alpha}$ or E_2 , oxytocin and zinc or copper salts of ethylene diamine tetraacetic acid.

The novel contraceptive compositions of this invention, in suitable dosage forms, comprise prostaglandin $F_{2\alpha}$ or E_2 , oxytocin and zinc or copper salts of ethylene diamine tetraacetic acid. These compositions are prepared in the form of a vaginal suppository and/or tampon by incorporating amounts of the active ingredients sufficient to prevent conception or implantation, without limiting side effects, first into a sustained release medium and then into a nontoxic conventional carrier according to accepted procedures. Preferably the compositions will contain, per dosage form, from about 100 μ g. to about 10 mg. of prostaglandin $F_{2\alpha}$ or E_2 , from about 1 μ g. to about 1000 μ g. of oxytocin, from about 10 mg. to about 1000 mg. of copper or zinc salt of ethylene diamine tetraacetic acid.

In preparing the suppository dosage form the zinc disodium ethylene diamine tetraacetic acid and half of the prostaglandin (the other half being dissolved in the biodegradable low melting wax or related substance to provide a slow release of the prostaglandin) are dissolved or suspended in water to make-up 10% of the total weight. The glycerin is then added mixing carefully to exclude incorporation of air bubbles. The mixture is heated on a water bath and the gelatin added and stirred until the gelatin is dissolved. The mixture is then allowed to cool and the powdered cetyl palmitate is stirred in and the total mixture is poured into chilled non-lubricated molds and allowed to stand until congealed. A similar procedure is used for the carbowax suppositories, or theobroma oil may be substituted. Thus the suppositories are prepared following the conventional techniques of the pharmaceutical chemist.

To prepare the tampon dosage form, the active ingredients (a), (b), (c) and (d) used in the glycerin suppository example below are dissolved or suspended in 5 ml. of water and absorbed into a cylinder of hydrophilic polyurethane foam measuring approximately 1.5" in diameter and approximately 3" long. The water is then evaporated *in vacuo* or freeze dried, and the impregnated cylinder is used as a vaginal tampon.

Cellulose tampons are well-known in the art. Conventional polyurethane foams are the reaction product of liquid polyols (polyether or polyester) and a difunctional isocyanate, usually toluene diisocyanate. A catalyst such as tin, an amine, a flowing agent, generally water, and foaming stabilizers are also employed. The required cylinders for tampon use are cut from the prepared foam.

The method in accordance with this invention comprises inserting in the animal organism one vaginal suppository and/or impregnated tampon between one hour and twenty-four hours after exposure to conception to prevent conception or implantation. The above application is repeated every 24 hours for one to seven days following the initial exposure. In cases where both the suppository and the tampon are used, the suppository is inserted first and then held in position by the tampon. If the vaginal suppository is used alone, a nonimpregnated tampon should be in-

serted immediately afterward to hold the contents in place. Carrying out the methods as described above reliably prevents conception or implantation with a minimum of side effects.

The preferred prostaglandins are PGF_{2a} and PGE_2 as luteolytic agents. The preferred ethylene diamine tetraacetic acid salts are the zinc disodium salt and the copper disodium salt, as antizygotic agents.

Inasmuch as the prostaglandins have a half life in blood serum of only ten minutes, it is necessary that a portion of the prostaglandin in the suppository or tampon be in a slow release form. This is accomplished by dissolving or suspending the prostaglandin in a melt of low melting, biodegradable wax. The wax with the prostaglandin incorporated is then either powdered, or the melt is poured over a cold surface and the waxy material scraped off in the form of powder or flakes. Among the vehicles for slow release of prostaglandin in biological fluids are cetyl palmitate, carnauba wax, lauric acid, a mixture of sodium laurate and lauric acid, a mixture of stearic acid and sodium stearate, a mixture of arachidonic acid and sodium arachidonate, and cetyl palmitate. Arachidonic acid has the further advantage of being a precursor of prostaglandin F_{2a} and prostaglandin E_2 in seminal tissue, and hence it can contribute to the prostaglandin levels made available from the suppository or tampon.

The following examples illustrate the preparation of compositions of this invention and as such are not to be considered as limiting the invention set forth in the claims appended hereto.

EXAMPLE 1

Ingredients	G./suppository
Glycerin	3.5
Gelatin, granular	1.0
Water plus	
(a) 200 μg . PGF_{2a}	
(b) 10 μg . oxytocin	
(c) 100 mg. of zinc salt of ethylene diamine tetraacetic acid adjusted to neutral pH aa q.s. ad	0.5
(d) 200 μg . PGF_{2a} and 10 μg . oxytocin dissolved in 0.5 gm. of melted cetyl palmitate which is then powdered after cooling	0.5
	5.5

The active ingredients (a), (b), (c) and (d) are dissolved or suspended in water to make up 10% of the total weight. The glycerin is added, mixing carefully to exclude incorporation of air bubbles. The mixture is heated on a water bath, the gelatin is added and then stirred until the gelatin is dissolved. This mixture is poured into chilled non-lubricated molds and allowed to stand until congealed to give a vaginal suppository.

The 400 μg . of PGF_{2a} may be replaced with the same amount of PGE_2 , and the zinc salt of ethylene diamine tetraacetic acid may be replaced by the copper salt.

EXAMPLE 2

Ingredients	G./suppository
Carbowax polyethylene glycol 6000	2.5
Carbowax polyethylene glycol 1540	1.5
Water plus	
(a) 200 μg . PGF_{2a}	
(b) 10 μg . oxytocin	
(c) 100 mg. of zinc salt of ethylene diamine tetraacetic acid adjusted to neutral pH aa q.s. ad	1.0
(d) 200 μg . PGF_{2a} and 10 μg . oxytocin dissolved in 0.5 gms. of melted cetyl palmitate which is then powdered after cooling	0.5
	5.5

The carbowax suppositories are prepared following the procedure described in Example 1. The 400 μg . of PGF_{2a} may be replaced with the same amount of PGE_2 , and the zinc salt of ethylene diamine tetraacetic acid may be replaced by the copper salt.

EXAMPLE 3

Ingredients

Water plus

- 200 μg . PGF_{2a} —5 g./tampon
- 10 μg . oxytocin
- 100 mg. of copper salt of ethylene diamine tetraacetic acid adjusted to neutral pH
- 200 μg . PGE_2 and 10 μg . of oxytocin dissolved in 0.5 gm. of melted cetyl palmitate or similar waxy material which is then powdered after cooling

The active ingredients (a), (b), (c) and (d) are dissolved or suspended in water and absorbed into a cylinder of cellulose or hydrophilic polyurethane foam measuring about 1.5 inches in diameter and about three inches in length. The water is then evaporated *in vacuo* or freeze dried and the impregnated cylinder is used as a vaginal tampon.

The 400 μg . of PGE_2 may be replaced with the same amount of PGF_{2a} and the copper salt of ethylene diamine tetraacetic acid may be replaced by the zinc salt.

I claim:

1. A sustained release contraceptive composition for use in the form of a vaginal suppository or impregnated tampon comprising:

- from about 100 μg . to about 10 mg. of prostaglandin F_{2a} or E_2 ,
- from about 1 μg . to about 100 μg . of oxytocin and
- from about 10 mg. to about 1000 mg. zinc or copper salt of ethylene diamine tetraacetic acid; with a portion of (a) being dissolved or suspended in a low melting biodegradable wax.

2. A contraceptive composition according to claim 1 in the form of a vaginal suppository.

3. A contraceptive composition according to claim 1 in the form of an impregnated tampon.

4. A contraceptive composition according to claim 3 in which the impregnated tampon is cellulose.

5. A contraceptive composition according to claim 3 in which the impregnated tampon is a polyurethane foam.

6. A contraceptive composition according to claim 1 in which the amount of (a) is 400 μg ., (b) is 10 μg ., (c) is 100 mg.

7. A contraceptive composition according to claim 6 in which the prostaglandin is F_{2a} .

8. The method of preventing conception or implantation which comprises inserting into the vagina of a mammal a sustained release composition in the form of a vaginal suppository or impregnated tampon each containing:

- from about 100 μg . to about 10 mg. of prostaglandin F_{2a} or E_2 ,
- from about 1 μg . to about 1000 μg . of oxytocin, and
- from about 10 mg. to about 1000 mg. of zinc or copper salt of ethylene diamine tetraacetic acid; with a portion of (a) being dissolved or suspended in a low melting biodegradable wax.

9. The method according to claim 8 in which the insertion is 1 to 24 hours after exposure to conception.

10. The method according to claim 9 in which the insertion of the composition is repeated about every 24 hours for from 1 to 7 days following initial exposure to conception.

11. The method according to claim 10 in which both the suppository and tampon are inserted into the vagina.

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12. The method according to claim 10 in which the suppository is inserted into the vagina.

13. The method according to claim 10 in which the tampon is inserted into the vagina.

14. The method according to claim 8 in which the amount (a) is 400 μ g., (b) is 10 μ g., (c) is 110 mg.

15. The method according to claim 14 in which the prostaglandin is F_{2a}.

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SAM ROSEN, Primary Examiner

U.S. Cl. X.R.

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