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(54) Title: VAGINALLY ADMINISTERD ANTI-DYSRHYTHMIC AGENTS FOR TREATING PELVIC PAIN AND INFERTILITY

(57) Abstract: The invention relates to a pharmaceutical composition for relieving pelvic pain or infertility associated with uterine dysrhythmia. The composition includes a locally-administered anti-dysrhythmic treating agent and a bioadhesive extended-release carrier. The composition may be delivered in an extended release formulation that includes a bioadhesive, water-swellable , water-insoluble, cross-linked polycarboxylic acid polymer, such as polycarbophil. The treating agent may be a local anesthetic, such as lidocaine. The invention also relates to a method of treating or preventing pelvic pain, or treating or improving infertility, by inserting a mixture of an anti-dysrhythmic treating agent and a bioadhesive carrier into the vagina of the patient to be treated.

VAGINALLY ADMINISTERED ANTI-DYSRHYTHMIC AGENTS FOR TREATING PELVIC PAIN AND INFERTILITY

CROSS-REFERENCE TO RELATED APPLICATION

This application claims the benefit of U.S. Provisional Application No. 60/330,684, filed October 29, 2001, the content of which is expressly incorporated herein by reference thereto.

FIELD OF THE INVENTION

This invention relates to a pharmaceutical composition for treating or preventing pelvic pain associated with uterine dysrhythmia, as well as to a method for treating or preventing such pain. The composition and method focus in part on local, topical use of treating agents for absorption into local tissue to prevent or treat the underlying abnormal or undesireable muscle contractions that are causing the pain or discomfort rather than merely relieving or masking the resulting pain or discomfort without affecting the cause. The invention also relates to a pharmaceutical compostion for treating or improving infertility associated with uterine dysrhythmia, as well as to a method for treating or improving such infertility.

BACKGROUND OF THE INVENTION

Pelvic pain may be intermittent or recurrent, or it may be constant and severe, but it is frequently associated with uterine dysrhythmia -- abnormal, disordered, or disturbed contractions of the uterus. Pelvic pain is often experienced during menses, as painful menstruation, or dysmenorrhea. Women with chronic pelvic pain associated with menstruation frequently spend one day each month in bed and also may have an additional day each month of reduced activity because of the severity of the pain. Pelvic pain may also be caused by pelvic infections, and diseases of the urinary tract or bowel.

Infertility also may be associated with uterine dysrhythmic conditions, including dysmenorrhea. *See, e.g.*, U.S. Patent Application Ser. No. 10/089,796. Uterine dysrhythmias may affect the rapid transport of sperm, thus affecting fertility. Contractility along the female tract (uterus and fallopian tubes) appears to be the primary motor assuring rapid transport of sperm from the cervical area to the distal end of the tubes, where fertilization takes place. Retrograde uterine contractility appears to impede this normal transport mechanism.

Chronic pelvic pain is common in women in the reproductive age group. It causes disability and distress, and results in significant costs to health services. Overall, a woman has about a 5% risk of having chronic pelvic pain for some period of time in her lifetime. In patients with a previous diagnosis of pelvic inflammatory disease this risk is increased fourfold to approximately 20%. Recent epidemiologic data from the United States showed that 14.7% of women in their reproductive ages reported chronic pelvic pain. A total of 15% of these women with chronic pelvic pain reported time lost from work and 45% reported reduced work productivity. In the United States 10% of outpatient gynecologic consultations are for chronic pelvic pain and 40% of laparoscopies are done for chronic pelvic pain.

The pathogenesis of chronic pelvic pain is poorly understood. Often, investigation by laparoscopy may reveal endometriosis, mild to moderate, or it may reveal no obvious cause for pain. There are several possible explanations for chronic pelvic pain including undetected irritable bowel syndrome, the vascular hypothesis where pain is thought to arise from dilated pelvic veins in which blood flow is markedly reduced and altered spinal cord and brain processing of stimuli in women with chronic pelvic pain. As the pathophysiology of chronic pelvic pain is not well understood, its treatment is often unsatisfactory and limited to symptom relief. Currently, the main approaches to treatment include symptomatic treatment of pain with medication, surgery, or possibly psychotherapy and counseling.

Very little is known about effective pharmacologic treatment for chronic pelvic pain, despite the fact that it is a very common chronic pain syndrome. Several different pharmacologic classes of medications have been used to alleviate the symptomatic pain and discomfort, rather than treat or prevent the underlying cause, in patients with chronic pain syndromes: nonsteroidal anti-inflammatory drugs, anticonvulsants, local anesthetics, and opioids. Very few studies have focused on the actual treatment or prevention of the underlying cause -- uterine dyskinetic contractions -- in order to treat or prevent chronic pelvic pain.

Dysmenorrhea is associated with pain typically related to the menstrual cycle and can be primary or secondary. Most women experience primary dysmenorrhea at some time during their life. The pain is cramping or sharp and lasts the first few days of the menstrual period. It may radiate to the back, thighs, or deep pelvis. Occasionally, nausea or vomiting occurs. Secondary dysmenorrhea may be due to endometriosis or cervical

stenosis or, if associated with heavy menstrual flow, to fibroids, adenomyosis, or large endometrial polyps.

In order to provide local or regional blockade for extended periods, clinicians currently use local anesthetics administered through a catheter or syringe to a site where the pain is to be blocked. This requires repeated administration where the pain is to be blocked over a period of greater than one day, either as a bolus or through an indwelling catheter connected to an infusion pump. These methods have the disadvantage of potentially causing irreversible damage to nerves or surrounding tissues due to fluctuations in concentration and high levels of anesthetic. In addition, anesthetic administered by these methods are generally neither confined to the target area, nor delivered in a linear, continuous manner. In all cases, analgesia rarely lasts for longer than six to twelve hours, more typically four to six hours. In the case of a pump, the infusion lines are difficult to position and secure, the patient has limited, encumbered mobility and, when the patient is a small child or mentally impaired, may accidentally disengage the pump.

U.S. Patent No. 5,700,485 discloses a method and device for administering a local anesthetic combined with a biodegradable polymer incorporated into microspheres. Prolonged release of the anesthetic is obtained by administration with glucocorticoid.

Because high systemic anesthetic concentration can cause irritation or burning to the vagina, as well as other detrimental side effects, there is a need to keep systemic circulation of the anesthesia low. Thus, there is a need for a formulation in which local anesthetics would diffuse preferentially into the cervix for a prolonged period of time to ensure sufficient anesthesia for treating pelvic pain due to dysrhythmic conditions, while keeping systemic circulation low.

Similarly, high systemic levels of other anti-dysrhythmic treating agents may lead to adverse side effects, some of which may be severe. Many classic anti-arrhythmic (and other anti-dysrhythmic) agents themselves have the ability to cause coronary arrhythmia. Other detrimental side effects include without limitation nausea, blurred or yellow vision, precipitation of glaucoma, constipation, seizures, tremor, bone marrow aplasia, pulmonary fibrosis, hypotension, reduction of exercise heart rate, diarrhea and diarrhea-induced hypokalemia, and immunological reactions such as thrombocytopenia, hepatitis, or bone marrow depression. Thus, use of an anti-dysrhythmic agent to treat or prevent uterine dysrhythmia must carefully avoid systemic levels that could prompt coronary problems or other adverse side effects.

Accordingly, there is a need for a formulation that would locally and preferentially deliver anti-dysrhythmic treating agents to treat or prevent pelvic pain due to dysrhythmia, or to treat or improve infertility associated with dysrhythmia. The formulation should avoid blood levels of the treating agent high enough to cause detrimental side effects, while attaining sufficient local tissue levels of the treating agent to provide the desired therapeutic anti-dysrhythmic effect.

SUMMARY OF THE INVENTION

The invention relates to a pharmaceutical vaginal composition for treating or preventing pelvic pain associated with uterine dysrhythmia, or for treating or improving infertility associated with uterline dysrhythmia, comprising a therapeutically effective amount of an anti-dysrhythmic treating agent and a pharmaceutically acceptable extended-release bioadhesive carrier.

The invention also relates to a method of treating or preventing pelvic pain, or for treating or improving infertility, comprising vaginally administering a composition that comprises a therapeutically effective amount of an anti-dysrhythmic treating agent and a pharmaceutically acceptable bioadhesive carrier that releases the treating agent over an extended period of time after administration.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to a pharmaceutical composition that includes an effective amount of a treating agent, intended to reduce or relieve uterine dysrhythmia by normalizing propagation of the nerve impulses and/or nerve impulses or cell to cell communication (*i.e.*, faster, slower, or more consistent) causing the abnormal or undesireable contractions, together with a pharmaceutically acceptable bioadhesive carrier. Such anti-dysrhythmic treating agents include local anesthetics, classic "antiarrhythmics" normally associated with use for treating coronary dysrhythmias, calcium channel blockers, and autocoid agents such as prostaglandins and prostaglandin blockers, non-steroidal anti-inflammatory drugs ("NSAIDS"), COX inhibitors, thromboxane synthase inhibitors, and leukotriene inhibitors.

Local anesthetics are generally defined as a drug which may be used to provide local numbness or pain relief, by preventing the propagation of nerve impulses that relay or report the sensation of pain. Local anesthetics useful with the instant invention

may include any such anesthetic known to one of ordinary skill in the art. Lidocaine is a preferred anesthetic for use with the present invention. Other local anesthetics that may be used include cocaine, chloroprocaine, tetracaine, prilocaine, mepivacaine, buipivacaine, levobupivacaine, articaine, ropivacaine, phenol, benzocaine, pramoxine, dyclonine, etidocaine, procaine, proparacaine, dibucaine, and pramoxine.

Classic anti-arrhythmics are generally used for treating or preventing coronary arrhythmias. Such treating agents include, for example, lidocaine, phenytoin, mexiletine, tocainide, procainamide, quinidine, disopyramide, moricizine, propafenone, flecainide, sotalol, bretyllium, amiodarone, verapamil, diltiazem, digoxin, digitoxin, adenosine, propranolol, esmolol, and N-acetyl procainamide.

Calcium channel blockers are used as coronary anti-arrhythmic agents due to their actions on SA and AV nodes. These agents tend also to decrease coronary vascular resistance and increase coronary blood flow. Examples of calcium channel blockers include, without limitation, amlodipine, bepridil, diltiazem, felodipine, isradipine, nicardipine, nifedipine, nimodipine, and verapamil. The most common side effects tend to be caused by excessive vasodilation, and may cause dizziness, hypotension, headache, digital dysesthesia, and nausea. Other side effects include constipation, aggrevation of myocardial ischemia, and peripheral or pulmonary edema.

Prostaglandins and related compounds are called eicosanoids, because of their common structural derivation. Eicosanoids also include leukotrienes and thromboxane A_2. Prostaglandins often are potent vasodilators and/or vasoconstrictors. Certain prostaglandins reduce systemic blood pressure and increase blood flow to most organs, while others generally increase cardiac output. Leukotrienes tend to reduce coronary blood flow and thromboxane A_2 is a potent vasoconstrictor.

Inhibitors of eicosanoids or eicosanoid biosynthesis include prostaglandin blockers, thromboxane synthase inhibitors, leukotriene inhibitors, NSAIDS (Non-Steroidal Anti-Inflammatory Drugs), and COX inhibitors. Blocking or interfering with biosynthesis or bioactivity of various eicosanoids or eicosanoid precursors may also increase or decrease the number of contractions, not affecting the rhythm. This may occur through an indirect mechanism by affecting a peripheral or preliminary activity or synthesis.

Thromboxane synthase inhibitors include, for example, pirmagrel and dazoxiben.

Leukotriene inhibitors include, for example, zileuton.

NSAIDS include, for example, diclofenac, etodolac, fenoprofen, lurbiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, meclofenamate, fenamic acid, meloxicam, nabumetone, naproxin, oxaprozin, piroxicam, sulindac, and tolmetin.

COX inhibitors include, for example, aspirin, celecoxib, rofecoxib, and valdecoxib.

The bioadhesive carrier includes a bioadhesive, water-swellable, water-insoluble, cross-linked polycarboxylic polymer. A preferred carrier, which may be in a gel formulation, contains a polycarbophil base designed to give controlled, extended release of the local anesthetic through the vaginal mucosa. Similar formulations for administration of different treating agents for other purposes are described in U.S. Patent Nos. 5,543,150 and 6,126,959, the contents of which are each expressly incorporated herein by reference.

U.S. Patent No. 5,543,150 discloses and claims use of similar extended-release vaginal formulations with progesterone to provide a FIRST UTERINE PASS EFFECT: directed, local delivery of the progesterone to effect secretory transformation of the endometrium while maintaining very low blood serum levels of progesterone. Similarly, U.S. Patent No. 6,126,959 discloses and claims use and composition of other similar extended release formulations for vaginal delivery of treating agents to effect local efficacy without also causing detrimental blood levels of the treating agent.

The invention also relates to a method for treating or preventing pelvic pain that includes administering the composition vaginally. Such administration demonstrates a therapeutic benefit for treating or preventing pelvic pain associated with uterine dysrhythmia.

The invention also relates to a method for treating or improving infertility that includes administering the composition vaginally. Such administration demonstrates a therapeutic benefit for treating or improving infertility associated with uterine dysrhythmia.

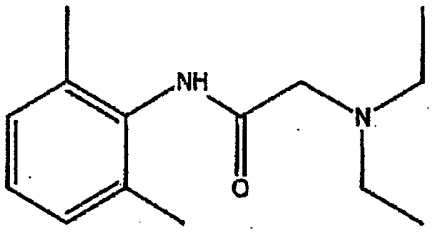
Preferably, the composition is administered in dosages that contain about 1% to 12.5% concentrations of the treating agent. For example, lidocaine may be administered as the treating agent in dosage concentrations of 2%, 5%, and 10%.

The composition of the invention is to be applied vaginally, and may be formulated as any appropriate vaginal composition, such as, without limitation, a gel or cream, or even as a gelifying tablet for administration. When administered, the composition diffuses through the vaginal mucosal into the target tissue. Relief from pain is provided by

treatment or prevention of the cause or source of the pain, *e.g.*, increased or dysrhythmic contractility.

The treating agents in the instant compositions diffuse in high concentrations into the myometrium to alter dysfunctional uterine contractility for control of pain associated therewith. Systemic circulation of the treating agent remains at a low level, enabling the treatment to avoid adverse systemic side effects. Depending on both the treating agent and the formulation, which can be modified to extend or shorted the duration of release of the treating agent, the release and efficacy of the treating agent may easily last for at least about 48 hours or more.

A preferred local anesthetic for use with the present invention is lidocaine. Lidocaine is an antidysrhythmic agent – as are most local anesthetics. Its chemical formula is 2-(diethylamino)-N-(2,6-dimethylphenyl) acetamide. Its molecular weight is 234.34. Its structural formula is:



Lidocaine is an extremely safe, effective anesthetic when it is delivered locally to the site of action -- though significant blood serum levels of lidocaine may also cause adverse side effects. It has a half-life of about 1.5 to 2 hours, which is sufficiently long to make it practical to use in sustained release formulations.

The specific drug delivery formulation chosen includes a cross-linked polycarboxylic acid polymer formulation, generally described in U.S. Patent No. 4,615,697 ("the '697 patent"), the content of which is expressly incorporated herein by reference thereto. In general, at least about 80% of the monomers of the polymer in such a formulation should contain at least one carboxyl functionality. The cross-linking agent should be present at such an amount as to provide enough bioadhesion to allow the system to remain attached to the target epithelial surfaces for a sufficient time to allow the desired dosing to take place. Of course, higher doses can be formulated readily by one of skill in the art to be released more slowly over a longer period of time; the key factor is the amount

of treating agent administered per unit time, while the concentration of the formulation can be varied inversely with the amount of formulation per unit dosage, or varied directly with the duration of release of the treating agent. In other words, a higher concentration of treating agent in the formulation can be delivered more slowly, and/or in a smaller dose of the formulation, to achieve the same overall rate of delivery of the treating agent.

For vaginal administration, the formulation preferably remains attached to the epithelial surfaces for a period of about 24 to 48 hours. Such results may be measured clinically over various periods of time, by testing samples from the vagina for pH reduction due to the continued presence of the polymer. This level of bioadhesion is generally attained when the cross-linking agent is present at about 0.1 to 6 weight percent of the polymer, preferably about 1 to 2 weight percent. Bioadhesion can also be measured using commercially available surface tensiometers utilized to measure adhesive strength.

The polymer formulation can be adjusted to control the release rate of the local anesthetic, such as lidocaine, by varying the amount of cross-linking agent in the polymer. Suitable cross-linking agents include divinyl glycol, divinylbenzene, N,N-diallylacrylamide, 3,4-dihydroxy-1,5-hexadiene, 2,5-dimethyl-1,5-hexadiene, and similar agents.

A preferred polymer for use in such a formulation is Polycarbophil, U.S.P., which is commercially available from Noveon, Inc., of Cleveland, Ohio under the trade name NOVEON®-AA1. Polycarbophil is a polyacrylic acid cross-linked with divinyl glycol.

Other useful bioadhesive polymers that may be used in such a drug delivery system formulation are mentioned in the '697 patent. For example, these include polyacrylic acid polymers cross-linked with 3,4-dihydroxy-1,5-hexadiene, and polymethacrylic acid polymers cross-linked with divinyl benzene.

Typically, these polymers would not be used in their salt form, because this would decrease their bioadhesive capability. Divalent salts, such as calcium salts, cause the greatest decrease in bioadhesion. Monovalent salts, such as sodium salts, typically do not reduce bioadhesion as much.

Such bioadhesive polymers may be prepared by conventional free radical polymerization techniques utilizing initiators such as benzoyl peroxide, azobisisobutyronitrile, and the like. Exemplary preparations of useful bioadhesives are provided in the '697 patent.

The bioadhesive formulation may be in the form of a gel, cream, tablet, pill, capsule, suppository, film, or any other pharmaceutically acceptable form that adheres to the mucosa and does not wash away easily. The preferred formulation for the present invention is in the form of a gel.

Additionally, the additives taught in the '697 patent may be mixed in with the cross-linked polymer in the formulation for maximum desired efficacy of the delivery system or for the comfort of the patient. Such additives include, without limitation, one or more of the following: lubricants, plasticizing agents, preservatives, gel formers, tablet formers, pill formers, suppository formers, film formers, cream formers, disintegrating agents, coatings, binders, vehicles, coloring agents, odor controlling agents, humectants, viscosity controlling agents, pH-adjusting agents, and other similar, commonly-used agents.

The present composition may be delivered to the vagina in a variety of fashions as known in the art, such as (without limitation) plunger, douche, and manually. One method of delivery is to use a device similar to those described in U.S. Design Patents Nos. D345,211 and D375,352. These devices are oblong hollow tube containers, with one end capable of being opened and the other end containing most of the composition to be delivered in a sealed container that may be used relatively easily by the patient. Said containers also maintain the formulation and treating agent in a sealed, sterile environment until use. Upon use, such a container is opened and the open end is inserted into the vagina, while the other end is squeezed to deliver the contents of the container into the vagina.

The present invention thus may be used to treat the underlying cause of the pain by delivering sufficient quantity of the treating agent to the affected tissue for an extended period of time. The delivery system provides a constant source of the drug which achieves concentrations that affect contractility of the tissue, while keeping systemic concentrations low enough to avoid adverse effects.

The local anesthetic will generally be used in its basic or unprotonated form. In this form, the anesthetics are only slightly soluble in water. In another form, the anesthetics may be used as water-soluble salts, such as hydrochlorides. The unprotonated form of the anesthetic is necessary for diffusion through cellular membranes to reach the site of action. Cationic species interact preferentially with the Na^+ channels. In a preferred embodiment, the anesthetic is used in its basic form and is suspended in a gel or gelafying tablet for delivery.

Local anesthetics, such as lidocaine, act on the uterine muscle as an antiarrhythmic and reverse uterine dyskinesia as a means of preventing pain of uterine cramping associated with dyskinesia rather than frequency of contractions. The anesthetics also prevent endometriosis by limiting retrograde menses caused by dysrhythmic contractions, and may also aid sperm transport in women with infertility linked to mild endometriosis associated with dysmenorrhea.

Typical oral or injection forms of anesthetics would need to achieve high blood levels in order to reach uterine tissue levels sufficient to demonstrate anti-dysrhythmic efficacy. Even so-called "trigger-point" injections would tend to cause higher blood levels, and present distinct disadvantages with regard to convenience and comfort of administration when compared to the instant formulations.

EXAMPLES

The following exemplary formulations may be made according to the present invention. All ingredients are listed in percentage by weight.

	Ex. 1	Ex. 2	Ex. 3	Ex. 4	Ex. 5	Ex. 6
Lidocaine Hydrocloride USP	6.15	6.15	6.15	6.15	6.15	6.15
Polycarbophil USP	1.00	0.75	1.25	1.50	1.00	0.75
NATROSOL® 250 HHX	2.00	2.25	1.50	1.50	2.00	2.00
Glycerol USP/BP	12.90	12.90	12.90	12.90	15.00	12.90
Sorbic acid NF/EP	0.08	0.08	0.08	0.08	0.08	0.08
Methyl Hydroxybenzoate NF, EP	0.18	0.18	0.18	0.18	0.18	0.18
Purified water USP/EP	77.69	77.69	77.94	77.69	75.59	77.94

	Ex. 7	Ex. 8	Ex. 9	Ex. 10	Ex. 11
Lidocaine Hydrocloride USP	12.30	12.30	12.30	2.46	2.46
Polycarbophil USP	1.00	1.00	1.00	1.00	0.75
Carbopol 974P NF		1.00	1.50		
NATROSOL® 250 HHX	2.00	1.00		2.00	2.00
Glycerol USP/BP	12.90	12.90	12.90	12.90	12.90
Sorbic acid NF/EP	0.80	0.80	0.80	0.80	0.80
Methyl Hydroxybenzoate NF, EP	0.18	0.18	0.18	0.18	0.18
Purified water USP/EP	70.82	70.82	71.32	80.66	80.91

	Ex. 12	Ex. 13	Ex. 14	Ex. 15	Ex. 16	Ex. 17
Ibuprofen	2.50	2.50	2.50	2.50	2.50	2.50
Polycarbophil USP	1.00	0.75	1.25	1.50	1.00	0.75
NATROSOL® 250 HHX	2.00	2.25	1.50	1.50	2.00	2.00
Glycerol USP/BP	12.90	12.90	12.90	12.90	15.00	12.90
Sorbic acid NF/EP	0.08	0.08	0.08	0.08	0.08	0.08
Methyl Hydroxybenzoate NF, EP	0.18	0.18	0.18	0.18	0.18	0.18
Purified water USP/EP	81.34	81.34	81.59	81.34	79.24	81.59

	Ex. 18	Ex. 19	Ex. 20	Ex. 21	Ex. 22
Ibuprofen	5.00	5.00	5.00	1.25	1.25
Polycarbophil USP	1.00	1.00	1.00	1.00	0.75
Carbopol 974P NF		1.00	1.50		
NATROSOL® 250 HHX	2.00	1.00		2.00	2.00
Glycerol USP/BP	12.90	12.90	12.90	12.90	12.90
Sorbic acid NF/EP	0.80	0.80	0.80	0.80	0.80
Methyl Hydroxybenzoate NF, EP	0.18	0.18	0.18	0.18	0.18
Purified water USP/EP	78.12	78.12	78.62	81.87	82.12

	Ex. 23	Ex. 24	Ex. 25	Ex. 26	Ex. 27	Ex. 28
Diltiazem	2.50	2.50	2.50	2.50	2.50	2.50
Polycarbophil USP	1.00	0.75	1.25	1.50	1.00	0.75
NATROSOL® 250 HHX	2.00	2.25	1.50	1.50	2.00	2.00
Glycerol USP/BP	12.90	12.90	12.90	12.90	15.00	12.90
Sorbic acid NF/EP	0.08	0.08	0.08	0.08	0.08	0.08
Methyl Hydroxybenzoate NF, EP	0.18	0.18	0.18	0.18	0.18	0.18
Purified water USP/EP	81.34	81.34	81.59	81.34	79.24	81.59

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	Ex. 29	Ex. 30	Ex. 31	Ex. 32	Ex. 33
Diltiazem	3.50	3.50	3.50	1.25	1.25
Polycarbophil USP	1.00	1.00	1.00	1.00	0.75
Carbopol 974P NF		1.00	1.50		
NATROSOL® 250 HHX	2.00	1.00		2.00	2.00
Glycerol USP/BP	12.90	12.90	12.90	12.90	12.90
Sorbic acid NF/EP	0.80	0.80	0.80	0.80	0.80
Methyl Hydroxybenzoate NF, EP	0.18	0.18	0.18	0.18	0.18
Purified water USP/EP	79.62	79.62	80.12	81.87	82.12

A nonlimiting example of a suitable formulation for vaginal delivery of anti-dysrhythmics comprises polycarbophil, carbopol, NATROSOL®, glycerol, sorbic acid, methyl hydroxybenzoate, and purified water mixed with an anti-dysrhythmic, preferably lidocaine or ibuprofen.

Sorbic acid and methylhydroxybenzoate are preservatives, which may be substituted by other known preservatives, such as benzoic acid, propylparaben, or propionic acid.

Carbopol is a gel former, preferably Carbopol 974P, but may be substituted by other gel formers including, but not limited to Carbopol 934P, Carbopol 980, methyl cellulose or propyl cellulose.

NATROSOL® 250 HHX is a viscosity-enhancing agent, but may be substituted by other viscosity-enhancing agents, such as methyl cellulose or propyl cellulose.

Glycerol is a humectant; alternative humectants include, for example, propylene glycol and dipropylene glycol.

As will be apparent to those skilled in the art, the composition can be varied to affect certain properties. For example, the concentration of the bioadhesive polymer can be adjusted to provide greater or lesser bioadhesion. The viscosity can be varied by varying the pH or by changing the concentration of the polymer or gel former. The pH also can be varied as appropriate to affect the release rate or bioadhesiveness of the formulation. All ingredients are well known and readily available from supplier known in the industry.

Thus, the present invention provides uses and compositions for vaginal administration of anti-dysrhythmic agents to treat pelvic pain associated with dysrhythmia.

The extended-release formulations enable effective local treatment without also causing blood levels sufficient to induce adverse side effects.

Any and all publications and patent applications mentioned in this specification are indicative of the level of skill of those skilled in the art to which this invention pertains. All publications and patent applications mentioned herein are hereby incorporated by reference to the same extent as if each individual publication or application was specifically and individually indicated to be incorporated by reference.

It is to be understood that the invention is not to be limited to the exact configuration as illustrated and described herein. Accordingly, all expedient modifications readily attainable by one of ordinary skill in the art from the disclosure set forth herein, or by routine experimentation therefrom, are deemed to be within the spirit and scope of the invention as defined by the appended claims.

THE CLAIMS

What is claimed is:

1. A pharmaceutical vaginal composition for treating or preventing pelvic pain, or for treating or improving infertility, associated with uterine dysrhythmia comprising a therapeutically effective amount of an anti-dysrhythmic treating agent and a pharmaceutically acceptable extended-release bioadhesive carrier.

2. The composition of claim 1, wherein the carrier comprises a bioadhesive, water-swellable, water-insoluble, cross-linked polycarboxylic acid polymer.

3. The composition of claim 2, wherein the polymer comprises polycarbophil.

4. The composition of claim 2, wherein the anti-dysrhythmic treating agent comprises one or more agents selected from the group consisting of coronary anti-arrhythmic, local anesthetics, calcium channel blocker, autocoid agents, prostaglandin blockers, non-steroidal anti-inflammatory drugs, COX inhibitors, thromboxane synthase inhibitors, and leukotriene inhibitors.

5. The composition of claim 3, wherein the anti-dysrhythmic treating agent comprises one or more agents selected from the group consisting of cocaine, chloroprocaine, tetracaine, prilocaine, mepivacaine, buipivacaine, levobupivacaine, articaine, ropivacaine, phenol, benzocaine, pramoxine, dyclonine, etidocaine, procaine, proparacaine, dibucaine, pramoxine, lidocaine, phenytoin, mexiletine, tocainide, procainamide, quinidine, disopyramide, moricizine, propafenone, flecainide, sotalol, bretyllium, amiodarone, verapamil, diltiazem, digoxin, digitoxin, adenosine, propranolol, esmolol, N-acetyl procainamide, amlodipine, bepridil, diltiazem, felodipine, isradipine, nicardipine, nifedipine, nimodipine, verapamil, pirmagrel, dazoxiben, zileuton, diclofenac, etodolac, fenoprofen, lurbiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, meclofenamate, fenamic acid, meloxicam, nabumetone, naproxin, oxaprozin, piroxicam, sulindac, tolmetin, aspirin, celecoxib, rofecoxib, and valdecoxib.

6. The composition of claim 2, wherein the treating agent comprises lidocaine.

7. The composition of claim 5, wherein the treating agent is lidocaine at a concentration of about 2% to 10% by weight.

8. The composition of claim 5, wherein the composition is prepared so that a single dosage of about 1 to 1.5 g of the composition will release about 20 to 150 mg of lidocaine over at least about 24 hours after administration.

9. The composition of claim 8, wherein the composition is prepared so that a single dosage will release the treating agent over at least about 48 to 72 hours.

10. A pharmaceutical vaginal composition for treating or preventing pelvic pain, or for treating or improving infertility, associated with uterine dysrhythmia comprising a therapeutically effective amount of a local anesthetic treating agent and a pharmaceutically acceptable extended-release bioadhesive carrier.

11. The composition of claim 10, wherein the carrier includes a bioadhesive, water-swellable, water-insoluble, cross-linked polycarboxylic acid polymer.

12. The composition of claim 11, wherein the treating agent is lidocaine.

13. The composition of claim 12, wherein the polymer is polycarbophil.

14. A method of treating or preventing pelvic pain, or for treating or improving infertility, comprising vaginally administering a composition that comprises a therapeutically effective amount of an anti-dysrhythmic treating agent and a pharmaceutically acceptable bioadhesive carrier that releases the treating agent over an extended period of time after administration.

15. The method of claim 14, wherein the treating agent is delivered and released over at least 24 hours.

16. The method of claim 15, wherein the treating agent is delivered and released over at least 48 hours.

17. The method of claim 16, wherein the treating agent is delivered and released over at least 72 hours.

18. The method of claim 15, wherein the carrier comprises a bioadhesive, water-swellable, water-insoluble, cross-linked polycarboxylic acid polymer.

19. The method of claim 18, wherein the carrier comprises polycarbophil and the treating agent comprises lidocaine.

20. The method of claim 18, wherein the treating agent is lidocaine and the lidocaine is administered in a dosage that releases about 20 to 100 mg of lidocaine over at least about 48 hours.

21. The method of claim 20, wherein the composition is administered about every 2 to 3 days to treat or prevent pelvic pain.

22. The method of claim 14, wherein the treating agent is a local anesthetic and the carrier comprises a bioadhesive, water-swellable, water-insoluble, cross-linked polycarboxylic acid polymer.

23. The method of claim 22, wherein the treating agent is lidocaine and the carrier comprises polycarbophil.

24. The method of claim 18, wherein the treating agent comprises one or more agents selected from the group consisting of cocaine, chloroprocaine, tetracaine, prilocaine, mepivacaine, buipivacaine, levobupivacaine, articaine, ropivacaine, phenol, benzocaine, pramoxine, dyclonine, etidocaine, procaine, proparacaine, dibucaine, pramoxine, lidocaine, phenytoin, mexiletine, tocainide, procainamide, quinidine,

disopyramide, moricizine, propafenone, flecainide, sotalol, bretyllium, amiodarone, verapamil, diltiazem, digoxin, digitoxin, adenosine, propranolol, esmolol, N-acetyl procainamide, amlodipine, bepridil, diltiazem, felodipine, isradipine, nicardipine, nifedipine, nimodipine, verapamil, pirmagrel, dazoxiben, zileuton, diclofenac, etodolac, fenoprofen, lurbiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, meclofenamate, fenamic acid, meloxicam, nabumetone, naproxin, oxaprozin, piroxicam, sulindac, tolmetin, aspirin, celecoxib, rofecoxib, and valdecoxib.

25. A pharmaceutical vaginal composition for treating or preventing uterine dysrhythmia comprising a pharmaceutically acceptable extended-release bioadhesive carrier and one or more treating agents selected from the group consisting of coronary anti-arrhythmic, local anesthetics, calcium channel blocker, autocoid agents, prostaglandin blockers, non-steroidal anti-inflammatory drugs, COX inhibitors, thromboxane synthase inhibitors, and leukotriene inhibitors.

26. The composition of claim 25 wherein the carrier comprises a bioadhesive, water-swellable, water-insoluble, cross-linked polycarboxylic acid polymer, and the one or more treating agents are selected from the group consisting of local anesthetics, NSAIDS, and calcium channel blockers.

27. The composition of claim 27 wherein the polymer is polycarbophil and the one or more treating agents include lidocaine.

28. A pharmaceutical vaginal composition comprising an anti-dysrhythmic treating agent and a pharmaceutically acceptable extended-release bioadhesive carrier, for use in a method of treatment of the human or animal body by therapy.

29. A pharmaceutical vaginal composition comprising a therapeutically effective amount of a local anesthetic treating agent and a pharmaceutically acceptable extended-release bioadhesive carrier, for use in a method of treatment of the human or animal body by therapy.

30. Use of an anti-dysrhythmic treating agent and a pharmaceutically acceptable extended-release bioadhesive carrier in the manufacture of a medicament for vaginal administration in the treatment or prevention of pelvic pain, or in improving infertility, wherein the pain or infertility is associated with uterine dysrhythmia.

31. Use of a local anesthetic treating agent and a pharmaceutically acceptable extended-release bioadhesive carrier in the manufacture of a medicament for vaginal administration in the treatment or prevention of pelvic pain, or in improving infertility, wherein the pain or infertility is associated with uterine dysrhythmia.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 02/12042

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K47/32 A61K9/00 A61K31/167 A61P15/02

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 91 06290 A (RIKER LABORATORIES INC) 16 May 1991 (1991-05-16) page 4, line 27 page 5, line 33 - line 36 page 11, line 35 -page 12, line 3 page 12, line 4 - line 5 page 12, line 13 - line 14 page 12, line 21 page 12, line 29 page 13, line 7 --- -/--	1-5,10, 11,25, 26,28,30

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
21 January 2003	30/01/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Giacobbe, S

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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X	WO 99 15210 A (HOUZE DAVID ;MANTELLE JUAN (US); KANIOS DAVID (US); NOVEN PHARMA () 1 April 1999 (1999-04-01) page 9, line 35 page 10, line 33 page 17, paragraph 12 page 19, paragraph 23 page 19, paragraph 24 page 30, paragraph 47 page 39, paragraph 78	1-5,25, 26,28,30
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Y	claim 14	1-5,10, 11, 14-18, 22, 24-26, 28-31
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INTERNATIONAL SEARCH REPORT

International Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 96 10989 A (BOLOGNA WILLIAM JOSEPH ;LEVINE HOWARD LESLIE (US)) 18 April 1996 (1996-04-18) page 3, line 15 -page 6, line 5	1-5,10, 11, 14-18, 22, 24-26, 28-31
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 02/12042

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 14-24 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
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