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(71) Applicant: WILLIAM H. RORER, INC. [US/US]; 500 Virginia Drive, Fort Washington, PA 19034 (US).

(72) Inventors: MIR, Ghulam, Nabi; P.O. Box 394, Buckingham, PA 18912 (US). KREBS, Jacqueline, Barbara; 1050 Byberry Road, Huntingdon Valley, PA 19006 (US). STUDT, William, Lyon; 611 Store Road, Harleysville, PA 19438 (US).

(74) Agent: SZOKE, Ernest, G.; 12 South Twelfth Street, Suite 3131, Philadelphia, PA 19107 (US).

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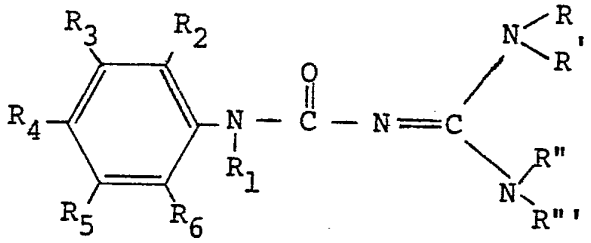
(54) Title: DYSMENORRHEA TREATMENT

(57) Abstract

Amidinoureas of the formula:



when administered to females who suffer dysmenorrhea relieve discomfort and pain and prevent damage caused by abnormal uterine muscle spasms incident to dysmenorrhea.

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DYSMENORRHEA TREATMENT

TECHNICAL FIELD:

This invention pertains to a novel method for inhibiting uterine muscle spasms associated with dysmenorrhea by the administration of amidinoureas.

BACKGROUND ART:

Dysmenorrhea or menstrual pain is the most common of all gynecological disorders in thirty to forty percent of post-pubescent females. Though the etiology of primary dysmenorrhea has not been established, it is known that dysmenorrheic subjects show evidence of a higher prostaglandin activity in their menstrual fluid. It is also known that prostaglandins have a powerful uterine stimulating activity, and many researchers believe that dysmenorrhea and menstrual pain from abnormal uterine muscle contraction are associated with the higher prostaglandin levels in dysmenorrhea subjects. Continued or prolonged dysmenorrhea may result in more severe disorders such as endometriosis.

In general, non-steriodal anti-inflammatory agents prevent the synthesis of prostaglandins and thus find some use in relieving pain in primary dysmenorrhea, but these drugs also prolong the bleeding time, due to their inhibition of platelet aggregation time.

Amidinoureas are known to have a variety of pharmacological effects and, in particular, certain substituted amidinoureas are disclosed in U.S. Patent 4,115,647 as having the property of producing a considerable spasmolytic action on the gastrointestinal musculature. Other amidino-

ureas have been described in U.S. Patent 4,060,635 as having anti-diarrheal properties which implies an antimotility effect related to spasmolytic action on the gastrointestinal musculature.

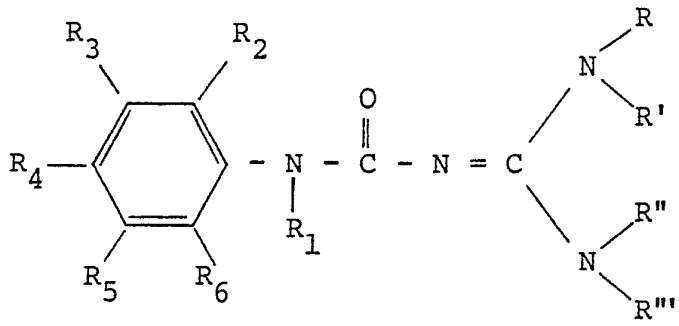
It has now unexpectedly been found that certain amidinoureas possess valuable pharmacological properties and these compounds exhibit an unexpected capability of inhibiting oxytocin and prostaglandin-induced contractions in In Vitro preparations. Abnormal uterine muscle contractions during the menstrual cycle in dysmenorrhea subjects are due to elevated levels of prostaglandin, therefore, certain amidinoureas will be efficacious in the treatment of dysmenorrhea. The amidinoureas appear to exert their activity on uterine muscle by acting beyond the prostaglandin receptor sites within the muscle membrane or contractile fiber which makes them particularly useful in the treatment of muscle spasms associated with primary dysmenorrhea. Depending on the particular situation, these amidinoureas may also inhibit prostaglandin-induced diarrhea, which at times accompanies dysmenorrhea.

It has also been found that these amidinoureas, which are easily absorbed from the stomach, have a low order of toxicity so that orally administering amidinoureas to females provides a simple and effective method for preventing and treating dysmenorrhea. Further, in accordance with this invention, a therapeutic program of treatment with an amidinourea can be the basis for relief from the pain of primary dysmenorrhea or, if started early in females having a tendency towards dysmenorrhea, amidinoureas administered continually in effective amounts can prevent the development of endometriosis and other severe conditions resulting from repeated dysmenorrhea.

DISCLOSURE OF INVENTION:

The present invention relates to a new method for inhibiting uterine muscle spasms associated with dysmenorrhea by the administration of amidinoureas. More particularly, the present invention describes a method for preventing and treating dysmenorrhea in humans or mammals by the

oral or parenteral administration of an effective amount of an amidinourea of Formula I below:



I

where:

R_2, R_3, R_4, R_5 and R_6 may be the same or different and are:

hydrogen
halo
lower alkyl
halo lower alkyl
nitro
lower alkoxy
hydroxy
arlower alkoxy
acyloxy
cyano
halo lower alkoxy, or
lower alkyl sulfonyl;

R and R' are hydrogen or lower alkyl;

R" and R"' are:

hydrogen
lower alkyl
lower alkoxy
lower alkenyl
cyclo alkenyl
cyclo alkyl lower alkyl
cyclo alkyl
aralkyl
lower alkynyl
halo alkyl
hydroxy alkyl
alkoxy alkyl

cyano alkyl
amino alkyl
mono- and di- lower alkyl amino alkyl
carbamoyl alkyl
mono- and di- carbamoyl alkyl
carboxy alkyl
alkoxy carbonyl alkyl
aralkoxy carbonyl alkyl
formyl
acyl
acyl alkyl
alkyl sulfonyl, or
aralkyl sulfonyl;

R" and R"' together may form a 5 to 7 atom ring which may include 0 to 2 hetero atoms of N, O or S; R_1 is hydrogen or it may be lower alkyl, provided at least one of R, R', R" and R"' is other than hydrogen;

and the nontoxic pharmaceutically acceptable salts thereof.

Compounds of this invention which are preferred include those where:

R_2, R_3, R_4, R_5 and R_6 are:
hydrogen
halo
lower alkyl
halo lower alkyl
nitro
hydroxy, or
lower alkoxy;

R' and R_1 are hydrogen or lower alkyl; and

R" and R"' are:
hydrogen
alkyl, or
alkoxy; provided R, R', R" and R"' are not all hydrogen at the same time.

The more preferred compounds of this invention include those where:

R_2 is hydrogen or lower alkyl;

R_3 and R_5 are:
hydrogen
hydroxy, or
lower alkoxy;

R_4 is:
hydrogen
lower alkyl
hydroxy
lower alkoxy, or
halo;

R_6 is:
hydrogen
lower alkyl
nitro
alkoxy, or
halo;

R and R_1 are hydrogen or lower alkyl; and
R' and R" are hydrogen or alkyl, provided R, R', R" and R"' are not all hydrogen at the same time.

The most preferred compounds of this invention are those where:

R_2 is:
hydrogen
methyl
ethyl
chloro, or
bromo;

R_3 is:
hydrogen
hydroxy, or
methoxy;

R_4 is:
hydrogen
methyl
ethyl
hydroxy
methoxy
chloro, or

bromo;

R_5 is:

hydrogen
hydroxy, or
methoxy;

R_6 is:

hydrogen
methyl
ethyl
nitro
methoxy
ethoxy
chloro
bromo, or
fluoro;

R and R_1 are:

hydrogen
methyl, or
ethyl; and

R' and R" are:

hydrogen
methyl
ethyl
propyl
i-propyl
butyl
i-butyl
sec-butyl
t-butyl
methoxy
ethoxy
propoxy
butoxy
isopropoxy
isobutoxy
t-butoxy
pentyl

hexyl, or

heptyl; provided R, R', R" and R"' are not all hydrogen at the same time.

A special embodiment of this invention comprises compounds which have:

R_2-lower alkyl substitution;

R_2, R_6-dilower alkyl substitution;

R_2, R_6-lower alkyl, alkoxy substitution;

R_2, R_6-lower alkyl, halo substitution;

R_2, R_6-alkyl, nitro substitution;

R_2, R_4, R_6-trilower alkyl substitution, or

R_2, R_4, R_6-lower alkyl, dihalo substitution.

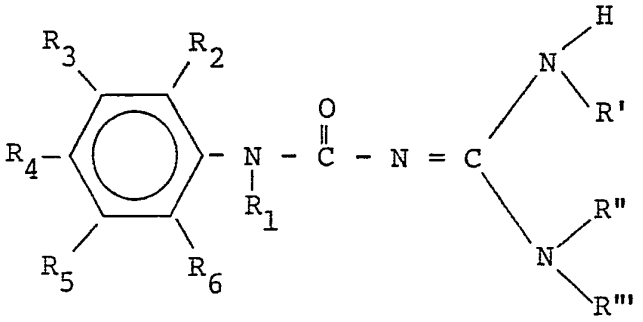
A further special embodiment of this invention comprises compounds which have:

R, R', R" and R"' as hydrogen or lower alkyl substitution, provided all are not hydrogen at the same time; or

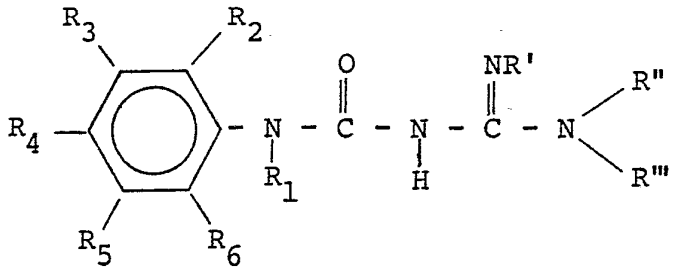
R and R' are hydrogen or lower alkyl and R" and R"' are an alkyl or alkoxy group from 3 to 7 carbon atoms.

The compounds of Formula I and the method of preparing them are described in U.S. Patent 4,060,635 and in Arzneimittel Forschung, 28(II), 1433-1480 (1978), the disclosures of which are incorporated herein by reference.

As is known, certain compounds of Formula I can exist in enolized or tautomeric forms or may be obtained as hydrates or in different polymorphic forms. Illustrative of tautomeric forms are the compounds of Formula I wherein R is hydrogen, in which case the compounds may exist in the alternative structural forms shown below:



Ia



IIa

It is understood that the designations of the amidinoureas suitable for use in the practice of this invention are intended to include the compounds specifically named or shown by structure along with the alternative or transient states where such exist. It is also intended to include the pharmaceutically acceptable salts of the amidinoureas designated by Formula I. Such salts include the nontoxic acid addition salts as well as other salts, for example, quarternary ammonium salts.

In accordance with this invention, it has now been found that amidinoureas of Formula I nonspecifically inhibit prostaglandin and oxytocin-induced uterine contractions without inhibiting blood platelet aggregation and, accordingly, these compounds can be used to reduce abnormal uterine contractions to normal physiological levels without affecting bleeding time in menstruating females. Furthermore, these compounds, when used in a regular therapeutic program for treating patients who suffer dysmenorrhea, can effectively prevent or alleviate secondary dysmenorrhea and the symptoms of secondary dysmenorrhea, especially endometriosis. Accordingly, these compounds are useful when administered in therapeutically effective amounts for the prevention or relief of primary dysmenorrhea and for the prevention or relief of endometriosis. For these purposes, they can be administered orally, parenterally, rectally, or intravaginally. Administration by the oral route is preferred. Orally, these compounds may be administered in tablets, hard or soft capsules, aqueous or oily suspensions, dispersible powders or granules, emulsions, syrups, or elixirs. The optimum dosage, of course, will depend on the particular compound being used and the type and severity of

the condition being treated. In any specific case, the appropriate dosage selected will further depend on factors of the patient which may influence response to the drug; for example, general health, age, weight, etc., of the subject being treated.

Although the optimum quantities for administration of the compounds of Formula I, in accordance with the present invention, will depend on the compound employed and the particular type of disease condition treated, oral dose levels of preferred compounds when administered to human or other mammalian females in dosages of 0.05 to 50 milligrams per kilogram of body weight per day are particularly useful. The preferred range is 0.1 to 20 mg/kg. Comparative dosages may be used in parenteral or rectal administration.

Compositions intended for oral use may be prepared according to methods known to the art for the manufacture of pharmaceutical compositions. Such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents, preserving agents, etc., in order to provide a pharmaceutically elegant and palatable preparation.

Further, the active amidinourea may be administered alone or in admixture with other agents having the same or different pharmacological properties. The compositions may contain such selected excipients such as inert diluents such as calcium carbonate, lactose, etc.; granulating and disintegrating agents such as magnesium stearate, etc.; binding agents such as starch,gelatin, etc.; suspending agents such as methylcellulose, vegatable oil, etc.; dispersing agents such as lecithin, etc.; thickening agents such as beeswax, hard paraffin, etc.; emulsifying agents such as naturally occurring gums, etc.; non-irritating excipients such as cocoa butter, polyethylene glycols, etc.; and the like. Further, in formulating these compounds, for every 100 parts by weight of the composition, there may be present between 5 and 95 parts by weight of the active ingredient. The dosage unit form will generally contain between 0.1 mg and about 500 mg of the active ingredient

of this invention. The preferred unit dose is between 1 mg and about 50 mg. The compositions may be taken 1 to 8 times daily depending on the dosage unit required.

In a preferred form, the compounds of this invention are prepared for oral administration in either tablet or capsule form, depending upon the solubility and capability of the specific amidinourea chosen and the other ingredients. In another preferred form, this invention is practiced by providing an effective amount of an amidinourea of Formula I, generally between about 5 and 10 mg in a single table or capsule suitable for oral administration to be administered about twice daily at a dose level of 1 to 2 tablets or capsules.

In general, the dosage regimen in carrying out the methods of this invention is that which insures maximum therapeutic response until improvement is obtained, and thereafter, the minimum effective level which gives relief. Generally, the daily dose can be between about 0.1 mg/kg and 70 mg/kg (preferably in the range of 1 to 25 mg/kg/day), bearing in mind, of course, that in selecting the appropriate dosage in any specific case, consideration must be given to the patient's weight, general health, age and other factors which may influence response to the drug.

Various tests in animals have been carried out to show the ability of the compounds of this invention to inhibit uterine muscle spasms. These tests involve the effect of the amidinoureas of Formula I on uterine muscle spasms in the presence of known spasmogens. It has been found that the compounds of this invention when tested in the above situations, show a marked activity.

Isolated Rat Uterine Muscle

Female virgin Wistar rats at an average weight of 160 g to 220 g are used for the experiment. Prior to the experiment, the animals are housed five per group and maintained according to standard animal husbandry procedures. The animals are treated with DES (100 mg/kg/body weight) 24 hours prior to the experiment. The stage of estrus cycle is determined by vaginal smears on the morning of the

experiment. Rats in estrus are killed by a blow on the head and the abdomen is opened. The two horns of the uterus are dissected out and transferred to a dish containing Bathing's solution (composition in g: NaCl, 8.046; KCl, 0.20; $CaCl_2 \cdot 2H_2O$, 0.132; $MgCl_2 \cdot 6H_2O$, 0.106; $NaHCO_3$, 1.0; NaH_2PO_4, 0.065; dextrose, 1.0 distilled to 1 liter with distilled water). The two horns are separated and freed from mesentery in Bathing's solution. A thread is attached at each end of each horn and the uterine segment is mounted in a tissue bath (50 ml), maintained at 37°C by a circulatory bath and aerated with 95% O_2 5% CO_2. One thread is attached to a fixed pin and the other to a transducer. Contractions are recorded isometrically on a Beckman dynograph in conjunction with a Grass force-displacement transducer (FTO3C) which has been calibrated in g. tension, or isotonically in conjunction with a Harvard smooth muscle transducer (386). The tissue is subjected to a baseline tension of 0.5 g. The preparation is allowed to equilibrate for 30 minutes prior to the experiment.

Various spasmogens (such as acetylcholine chloride, PGF_{2a}, PGE_2, oxytocin, $BaCl_2$ or ergonivine maleate) may be used to induce contractions in the isolated uterine strip. See "In Vitro Methodology for Evaluation of Compound Effect on Isolated Guinea Pig Ileum" for description of obtaining dose response curve. After the control dose response curve is obtained, the tissue is allowed to relax for five minutes before the addition of the spasmolytic drug (inhibitory drug). The test drug is in contact with the tissue for two minutes before the dose response curve is repeated. The inhibitory effect of the test drug is determined as follows:

$$\% \text{ maximum response} = \frac{\text{g tension developed with spasmogen + test drug}}{\text{g tension developed with spasmogen}} \times 100$$

The % maximum response is calculated for each dose of the dose response curve and the control and drug curves are plotted.

Effect of 1-(2',6'-dimethylphenyl)-3-methyl-amidinourea hydrochloride on Ach, oxytocin and PGF_{2a}-induced contractions in the gravid rat uterus

The dose response behavior on the isolated gravid rat uterus of acetylcholine chloride, oxytocin and PGF_{2a} was

compared in the presence and absence of varying doses of 1-(2',6'-dimethylphenyl)-3-methylamidinourea hydrochloride using the noncumulative dose response method. The stimulatory effect of these spasmogens on the isolated gravid rat uterus preparation was recorded using the isometric method to record the contractions induced (see Methodology). The inhibitory effect of 1-(2',6'-dimethylphenyl)-3-methylamidinourea hydrochloride on the spasmogen-induced contractions in the In Vitro gravid rat uterus preparation was demonstrated by increasing doses of 1-(2',6'-dimethylphenyl)-3-methylamidinourea hydrochloride. The inhibition by 1-(2',6'-dimethylphenyl)-3-methylamidinourea hydrochloride was dose dependent with all three spasmogens (see Tables).

TABLE I

% Inhibition of Ach-Induced Contractions by 1-(2',6'-dimethylphenyl)-3-methylamidinourea hydrochloride

Ach µg/ml	40 µg/ml*	80 µg/ml*	160 µg/ml*
20	100.0	100.0	100.0
40	83.0	100.0	100.0
80	79.7	100.0	100.0
160	46.8	95.8	100.0
320	2.8	26.8	93.3
640	<2.8	<26.8	93.6
1,280			84.6
2,560			67.4
5,120			61.2
10,240			62.7

*Concentration of 1-(2',6'-dimethylphenyl)-3-methylamidinourea hydrochloride

TABLE II

% Inhibition of Oxytocin-Induced Contractions by 1-(2',6'-dimethylphenyl)-3-methylamidinourea hydrochloride

Oxytocin U/ml	40 µg/ml*	80 µg/ml*	160 µg/ml*
1×10^{-5}	100.0	100.0	100.0

Table II (continued)

Oxytocin U/ml	40 µg/ml*	80 µg/ml*	160 µg/ml*
3×10^{-5}	22.1	100.0	100.0
1×10^{-4}	<22.1	48.7	100.0
3×10^{-4}		14.4	100.0
1×10^{-3}		<14.4	63.2
3×10^{-3}			47.6
			32.5

*Concentration of 1-(2',6'-dimethylphenyl)-3-methylamidinourea hydrochloride

TABLE III

% Inhibition of PGF_{2a}-Induced Contractions by 1-(2',6'-dimethylphenyl)-3-methylamidinourea hydrochloride

PGF_{2a_M}	40 µg/ml*	80 µg/ml*	160 µg/ml*
1×10^{-8}	99.0	98.2	100.0
3×10^{-8}	95.1	91.3	100.0
1×10^{-7}	39.5	64.0	98.5
3×10^{-7}	<39.5	48.9	96.1
1×10^{-6}		<48.9	91.1
3×10^{-6}			86.8

*Concentration of 1-(2',6'-dimethylphenyl-3-methylamidinourea hydrochloride

In view of the results of these tests, the pharmacological data clearly indicates that the amidinoureas of Formula I can be considered to be effective in inhibiting uterine muscle spasms associated with dysmenorrhea and are useful in preventing and treating dysmenorrhea or menstrual cramps.

Whereas Applicant has set forth herein what is believed to be the mode of action of the amidinoureas when used to treat primary dysmenorrhea or secondary dysmenorrhea, particularly endometriosis, it is to be understood that Applicant does not wish to be bound by any particular theory and the pharmacological tests and examples given herein are

by way of illustration only.

The following examples illustrate the preparation of tablets and capsules which constitute the preferred dosage forms for oral administration of the compounds of Formula I in accordance with the method of this invention.

Example 1

A batch of homogenous tablets was prepared, each having the following formula:

Per Tablet	Ingredients	Per 1000 Tablets
5 mg	1-(2',6'-dimethylphenyl)-3-methylamidinourea hydrochloride (lidamidine hydrochloride)	5 gm
100 mg	microcrystalline cellulose	100 gm
150 mg	cornstarch	150 gm
450 mg	deionized water	450 gm
10 mg	hydrogenated castor oil	10 gm
715 mg		715 gm

The following procedure is used to prepare the tablets: 1-(2',6'-dimethylphenyl)-3-methylamidinourea, cellulose and 100 gm of starch are blended together dry. A paste of the remaining starch is prepared with deionized water in a steam-jacketed pot. The two components are mixed, granulated and passed through a #8 screen, then dried in a fluid bed dryer at about 40°C and again passed through a #14 mesh screen. The composition is then formed into tablets by compressing on a Stokes rotary multi-layer tablet press.

Example 2

Therapeutic compositions of the invention are prepared by using known techniques for compounding, employing either the base or a salt as the active ingredient along with nontoxic excipients chosen in accordance with the particular form and properties desired for the therapeutic composition. Other therapeutic agents such as analgesics, tranquilizers, etc., may be added as desired.

Tablets which can be advantageously used for either remedial or prophylactic treatments for dysmenorrhea ordinarily accompanied by abnormal uterine muscle action can

be provided in a form which provides relief from dysmenorrhea symptoms when taken at a rate of 1 to 2 tablets twice daily containing about 5 to 10 mg of the active ingredient. An exemplary formulation which can be utilized is, for example, the following:

1-(2',6'-dimethylphenyl)-3-methylamidinourea	5 mg
tricalcium phosphate	200 mg
magnesium stearate	10 mg
talc	50 mg
polyvinyl acetate	40 mg

In addition, there are added protective excipients such as ethylcellulose, dibutylphthalate, propylene glycol, wax (white and/or carbauba), spermaceti, methylene chloride, and rectified diethyl ether. The ingredients are compressed to minimum size to provide a tablet of about 310 mg.

Example 3

A lot of 1,000 tablets each containing 1g of 1-(2',6'-diethylphenyl)-3-methylamidinourea is prepared from the following types and amounts of ingredients:

1-(2',6'-diethylphenyl)-3-methylamidinourea	10 g
dicalcium phosphate	1 kg
methylcellulose USP	75 kg
talc	150 g
cornstarch	200 g
magnesium stearate	10 g

The active ingredient and dicalcium phosphate are mixed thoroughly and granulated with a 7.5% solution of methylcellulose in water and passed through a #8 screen and air-dried. The dried granules are passed through a #12 screen and combined with the talc, starch and magnesium stearate with thorough mixing after which the composition is compressed into tablets.

Example 4

A lot of two-piece hard gelatin capsules, each containing 5 mg of 1-(2',6'-dimethylphenyl)-3-methylamidinourea are prepared from the following types and amounts of ingredients (the amounts given are per capsule):

1-(2',6'-dimethylphenyl)-3-methylamidinourea	5 g
dicalcium phosphate	500 g
talc	150 g
magnesium stearate	5 g

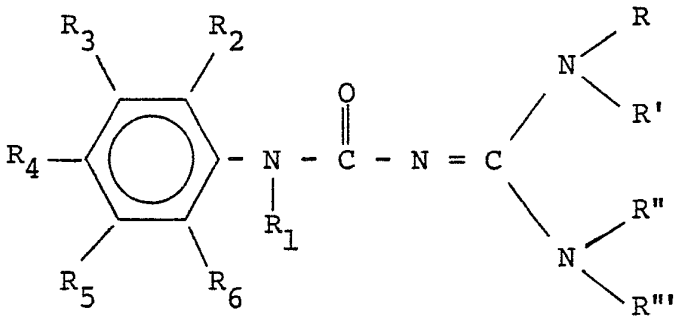
The ingredients are mixed thoroughly and filled into capsules which are used for oral administration at the rate of about one every four hours. If desired, slow release forms can be provided or delayed release forms depending on choice of capsules and formulating ingredients.

By analogous methods and employing techniques known to the art, there are prepared formulations suitable for administration of an effective amount of any of the amidinoureas of Formula I. In particular, by analogy of the processes described above, single dose preparations suitable for oral administration can be readily prepared from the following illustrative amidinoureas:

1-(2'-methyl-4,6'-dichlorophenyl)-3-methylamidinourea
1-(2'-chloro-6'-methylphenyl)-3-amidinourea hydrochloride
1-(2'-methyl-6'-bromophenyl)-3-amidinourea
1-(2'-methyl-6'-methoxyphenyl)-3-amidinourea hydrochloride
1-(2'-methyl-6'-ethylphenyl)-3-amidinourea
1-(2'-methyl-6'-methoxyphenyl)-3-methylamidinourea
1-(2',6'-dimethylphenyl)-3-amidinourea
1-(2',6'-diethylphenyl)-3-amidinourea
1-(2',6'-diethylphenyl)-3-methylamidinourea
1-(2',6'-dimethylphenyl)-3-methoxyamidinourea
1-(2',6'-diethylphenyl)-3-methoxyamidinourea.

CLAIMS:

1. A method for treating uterine muscle spasms associated with dysmenorrhea which comprises the oral or parenteral administration of an effective amount of an amidinourea of the general formula



where:

R_2, R_3, R_4, R_5 and R_6 may be the same or different and are:

hydrogen,
halo,
lower alkyl,
halo lower alkyl,
nitro,
lower alkoxy,
hydroxy,
arlower alkoxy,
acyloxy,
cyano,
halo lower alkoxy, or
lower alkyl sulfonyl;

R and R' are hydrogen or lower alkyl;

R" and R"' are:

hydrogen,
lower alkyl,
lower alkoxy,
lower alkenyl
cyclo alkenyl up to 9 carbon atoms,
cyclo alkyl lower alkyl,
lower alkyl,
cyclo alkyl,

aralkyl,
lower alkynyl,
halo alkyl,
hydroxy alkyl,
alkoxy alkyl,
cyano alkyl,
amino alkyl,
mono- and di- lower alkyl amino alkyl,
carbamoyl alkyl,
mono- and di- carbamoyl alkyl,
carboxy alkyl,
alkoxy carbonyl alkyl,
aralkoxy carbonyl alkyl,
formyl,
acyl,
acylalkyl,
alkyl sulfonyl, or
aralkyl sulfonyl;

R" and R"' together may form a 5 to 7 atom ring which may include 0 to 2 hetero atoms of N, O or S;

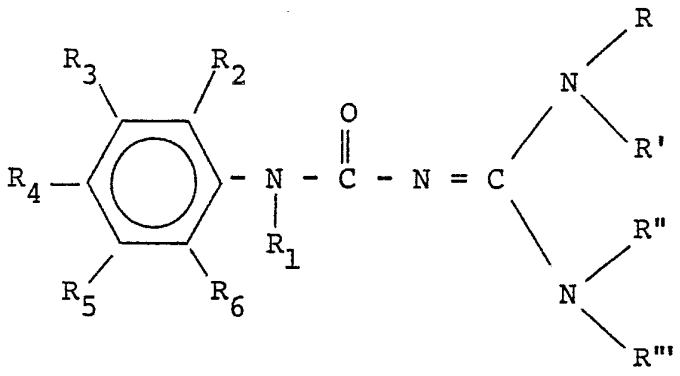
R_1 is hydrogen or lower alkyl, provided at least one of R, R', R" and R"' is other than hydrogen;

and the pharmaceutically acceptable salts thereof.

2. The method of Claim 1 wherein the amidinourea is 1-(2',6'-dimethylphenyl)-3-methylamidinourea.

3. The method of Claim 1 wherein the amidinourea is 1-(2',6'-dimethylphenyl)-3-methylamidinourea hydrochloride.

4. A method for the treatment of primary dysmenorrhea which comprises administering to a menstruating female an effective amount of an amidinourea of the formula



where:

R_2, R_3, R_4, R_5 and R_6 may be the same or different and are:

hydrogen,
halo,
lower alkyl,
halo lower alkyl,
nitro,
lower alkoxy,
hydroxy,
arlower alkoxy,
acyloxy,
cyano,
halo lower alkoxy, or
lower alkyl sulfonyl;

R and R' are hydrogen or lower alkyl;

R" and R"' are:

hydrogen,
lower alkyl,
lower alkoxy,
lower alkenyl,
cyclo alkenyl up to 9 carbon atoms,
cyclo alkyl lower alkyl,
lower alkyl,
cyclo alkyl,
aralkyl,
lower alkynyl,
halo alkyl,
hydroxy alkyl,
alkoxy alkyl,

cyano alkyl,
amino alkyl,
mono- and di- lower alkyl amino alkyl,
carbamoyl alkyl,
mono- and di- carbamoyl alkyl,
carboxy alkyl,
alkoxy carbonyl alkyl,
aralkoxy carbonyl alkyl,
formyl,
acyl,
acyl alkyl,
alkyl sulfonyl, or
aralkyl sulfonyl;

R" and R"' together may form a 5 to 7 atom ring which may include 0 to 2 hetero atoms of N, O or S;

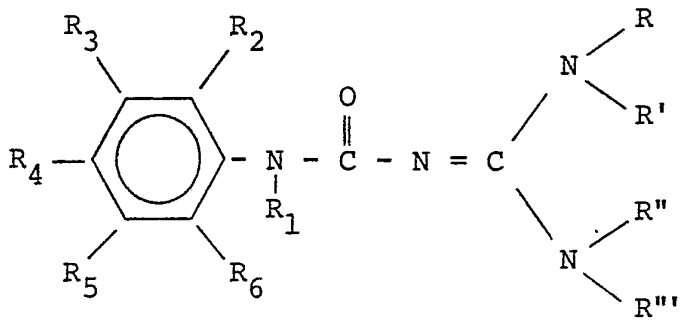
R_1 is hydrogen or lower alkyl, provided at least one of R, R', R" and R"' is other than hydrogen;

and the pharmaceutically acceptable salts thereof.

5. The method of Claim 4 wherein the amidinourea is 1-(2',6'-dimethylphenyl)-3-methylamidinourea.

6. The method of Claim 4 wherein the amidinourea is 1-(2',6'-dimethylphenyl)-3-methylamidinourea hydrochloride.

7. A method of reducing abnormal uterine muscle action to normal levels which comprises administering an effective amount of a compound of the formula



where:

R_2, R_3, R_4, R_5 and R_6 may be the same or different and are:

hydrogen,
halo,
lower alkyl,
halo lower alkyl,
nitro,
lower alkoxy,
hydroxy,
arlower alkoxy,
acyloxy,
cyano,
halo lower alkoxy, or
lower alkyl sulfonyl;

R and R' are hydrogen or lower alkyl;

R" and R"' are:

hydrogen,
lower alkyl,
lower alkoxy,
lower alkenyl,
cyclo alkenyl up to 9 carbon atoms,
cyclo alkyl lower alkyl,
lower alkyl,
cyclo alkyl,
aralkyl,
lower alkynyl,
halo alkyl,
hydroxy alkyl,
alkoxy alkyl,
cyano alkyl,
amino alkyl,
mono- and di- lower alkyl amino alkyl,
carbamoyl alkyl,
mono- and di- carbamoyl alkyl,
carboxy alkyl,
alkoxy carbonyl alkyl,
aralkoxy carbonyl alkyl,
formyl,

acyl,
acyl alkyl,
alkyl sulfonyl, or
aralkyl sulfonyl;

R" and R"' together may form a 5 to 7 atom ring which may include 0 to 2 hetero atoms of N, O or S;

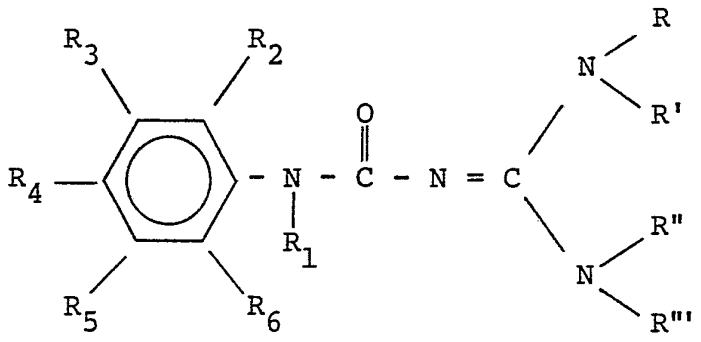
R_1 is hydrogen or lower alkyl, provided at least one of R, R', R" and R"' is other than hydrogen;

and the pharmaceutically acceptable salts thereof.

8. The method of Claim 7 wherein the amidinourea is 1-(2',6'-dimethylphenyl)-3-methylamidinourea.

9. The method of Claim 7 wherein the amidinourea is 1-(2',6'-dimethylphenyl)-3-methylamidinourea hydrochloride.

10. A method for preventing endometriosis which comprises administering to dysmenorrhea subjects an effective amount of a compound of the formula



where:

R_2, R_3, R_4, R_5 and R_6 may be the same or different and are:

hydrogen,
halo,
lower alkyl,
halo lower alkyl,
nitro,
lower alkoxy,
hydroxy,

arlower alkoxy,
acyloxy,
cyano,
halo lower alkoxy, or
lower alkyl sulfonyl;

R and R' are hydrogen or lower alkyl;

R" and R"' are:
hydrogen,
lower alkyl,
lower alkoxy,
lower alkenyl,
cyclo alkenyl up to 9 carbon atoms,
cyclo alkyl lower alkyl,
lower alkyl,
cyclo alkyl,
aralkyl,
lower alkynyl,
halo alkyl,
hydroxy alkyl,
alkoxy alkyl,
cyano alkyl,
amino alkyl,
mono- and di- lower alkyl amino alkyl,
carbamoyl alkyl,
mono- and di- carbamoyl alkyl,
carboxy alkyl,
alkoxy carbonyl alkyl,
aralkoxy carbonyl alkyl,
formyl,
acyl,
acyl alkyl,
alkyl sulfonyl, or
aralkyl sulfonyl;

R" and R"' together may form a 5 to 7 atom ring which may include 0 to 2 hetero atoms of N, O or S;

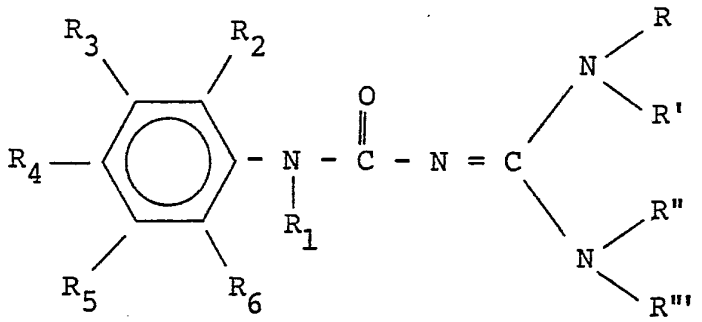
R_1 is hydrogen or lower alkyl, provided at least one of R, R', R" and R"' is other than hydrogen;

and the pharmaceutically acceptable salts thereof.

11. The method of Claim 10 wherein the amidinourea is 1-(2',6'-dimethylphenyl)-3-methylamidinourea.

12. The method of Claim 10 wherein the amidinourea is 1-(2',6'-dimethylphenyl)-3-methylamidinourea hydrochloride.

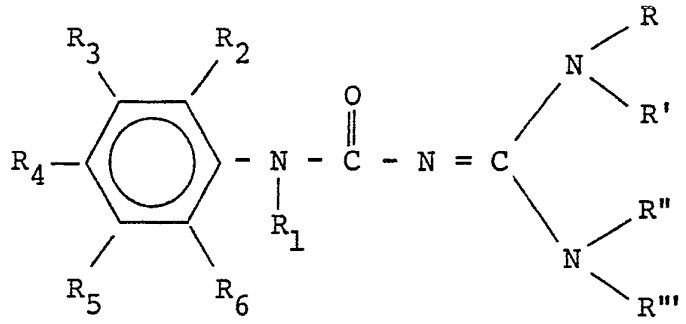
13. A method for the treatment of primary dysmenorrhea which comprises administering to a menstruating female an effective amount of a compound of the formula



wherein R_2, R_3, R_4, R_5 and R_6 are:
hydrogen,
halo,
lower alkyl,
halo lower alkyl,
nitro,
hydroxy, or
lower alkoxy;
R' and R_1 are hydrogen or lower alkyl; and
R" and R"' are:
hydrogen,
alkyl, or
alkoxy; provided R, R', R" and R"' are not all hydrogen at the same time;
and the nontoxic pharmaceutically acceptable salts thereof.

14. A method for the treatment of primary dysmen-

orrhea which comprises administering to a menstruating female an effective amount of a compound of the formula



wherein:

R_2 is hydrogen or lower alkyl;

R_3 and R_5 are:

hydrogen,

hydroxy, or

lower alkoxy;

R_4 is:

hydrogen,

lower alkyl,

hydroxy,

lower alkoxy, or

halo;

R_6 is:

hydrogen,

lower alkyl,

nitro,

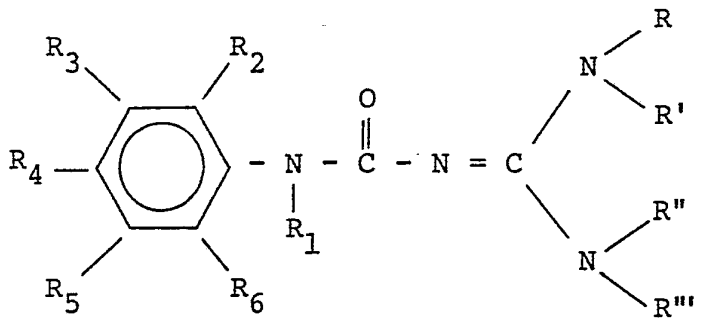
alkoxy, or

halo; and

R and R_1 are hydrogen or alkyl, provided R, R', R" and R"' are not all hydrogen at the same time;

and the nontoxic pharmaceutically acceptable salts thereof.

15. A method for the treatment of primary dysmenorrhea which comprises administering to a menstruating female an effective amount of a compound of the formula



wherein:

R_2 is:

hydrogen,
methyl,
ethyl,
chloro, or
bromo;

R_3 is:

hydrogen,
hydroxy, or
methoxy;

R_4 is:

hydrogen,
methyl,
ethyl,
hydroxy,
methoxy,
chloro, or
bromo;

R_5 is:

hydrogen,
hydroxy, or
methoxy;

R_6 is:

hydrogen,
methyl,
ethyl,
nitro,
methoxy,

ethoxy,
chloro,
bromo, or
fluoro;

R and R_1 are:
hydrogen,
methyl, or
ethyl; and

R' and R" are:
hydrogen,
methyl,
ethyl,
propyl,
i-propyl,
butyl,
i-butyl,
sec-butyl,
t-butyl,
methoxy,
ethoxy,
propoxy,
butoxy,
isopropoxy,
isobutoxy,
t-butoxy,
pentyl,
hexyl, or
heptyl; provided R, R', R" and R"' are not all hydrogen at the same time;

and the nontoxic pharmaceutically acceptable salts thereof.

16. The method according to Claim 15 wherein the compounds have:

R_2-lower alkyl substitution;
R_2, R_6-dilower alkyl substitution;
R_2, R_6-lower alkyl, alkoxy substitution;
R_2, R_6-lower alkyl, halo substitution;

R_2, R_6-alkyl, nitro substitution;

R_2, R_4, R_6-trilower alkyl substitution, or

R_2, R_4, R_6-lower alkyl, dihalo substitution.

17. The method according to Claim 16 wherein the compounds have:

R, R', R" and R"' as hydrogen or lower alkyl substitution provided all are not hydrogen at the same time; or,

R and R' are hydrogen or lower alkyl and R" and R"' are an alkyl or alkoxy group from 3 to 7 carbon atoms; and the non-toxic pharmaceutically acceptable salts thereof.

INTERNATIONAL SEARCH REPORT

International Application No PCT/US80/00344

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [3]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int. Cl. A61/K, 31/155, 31/17, 31/22,31/34,31/38, 31/40,31/275
US 424/244,267,274,275,285,304,311,322,326

II. FIELDS SEARCHED

Minimum Documentation Searched [4]

Classification System	Classification Symbols
US	424/244,267,274,275,285,304,311,322,326

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [5]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [14]

Category *	Citation of Document, [16] with indication, where appropriate, of the relevant passages [17]	Relevant to Claim No. [18]
A	US, A, 4,060,635 Published 29 November 1977 Diamond et al	1-17
A	US, A, 4,115,647 Published 19 September 1978 Douglas et al	1-17
A	Arzneimittel Forschung/Drug Research Vol. 28. (II) No. 8a, issued August, 1978 (West Germany), Lidamidine Hydrochloride (WHR-1142A), PP 1433-1480	1-17

* Special categories of cited documents: [15]

"A" document defining the general state of the art

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

"L" document cited for special reason other than those referred to in the other categories

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

"P" document published prior to the international filing date but on or after the priority date claimed

"T" later document published on or 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

IV. CERTIFICATION

Date of the Actual Completion of the International Search [2]

06 June 19

Date of Mailing of this International Search Report [2]

24 JUL 1980

International Searching Authority [1]

ISA/US

Signature of Authorized Officer [20]

Paul C. Wassel for
AMFagelson

Form PCT/ISA/210 (second sheet) (October 1977)