HRA Pharma
Laboratoire

May 5, 2003

Dockets Management Branch
Food and Drug Administration
Department of Health and Human Services
Rm. 1-23
12420 Parklawn Dr.
Rockville, MD 20857
USA

PETITION TO REQUEST A CHANGE FROM A LISTED DRUG

HRA Pharma submits this petition pursuant to 21CFR 314.93 to request that the Commissioner of Food and Drugs permit the filing of an Abbreviated New Drug Application (ANDA) for a drug that is not identical to the listed drug in strength.

ACTION REQUESTED

As provided in 21 C.F.R. § 314.93, we hereby request the Agency to permit the filing of an Abbreviated New Drug Application (ANDA) for a drug product (1.5 mg levonorgestrel tablet) which is not identical to the reference listed drug (Plan B® 0.75 mg levonorgestrel tablet) in strength.

STATEMENT OF GROUNDS

Section 505(j)(2)(C) of the Federal Food, Drug, and Cosmetic Act provides for the acceptance of an Abbreviated New Drug Application (ANDA) for a new drug which differs from a "listed" drug in dosage strength, under the condition that prior permission has been obtained from the FDA for such a submission via a suitability petition. 21 C.F.R. § 314.93(b). The Act stipulates that such a petition must be approved by the Agency unless there is a finding that investigations are needed to demonstrate the safety and effectiveness of the proposed drug product. In accordance with this provision, the present petition is presented to request permission to submit an ANDA for a 1.5 mg levonorgestrel tablet with the reference drug being Plan B®.

The listed drug in question is Plan B® (0.75 mg levonorgestrel tablet); the Orange Book listing for Plan B® is herewith attached in Appendix 1, and a copy of the approved labeling for Plan B® is herewith attached in Appendix 2. The new drug in question is a 1.5 mg levonorgestrel tablet, and a copy of proposed labeling for the proposed 1.5 tablet is herewith attached in Appendix 3. As evidenced by both drug's labeling, the active ingredient of both the proposed and the reference listed drug is identical, that being levonorgestrel (d-norgestrel, 13β-ethyl-17β-hydroxy-18,19-dinor-17α-pregn-4-en-20-yn-3-one, CAS N° 797-63-7).

The dosage and administration of Plan B® calls for the intake of a total dose of 1.5 mg levonorgestrel, administered as two tablets of 0.75 mg levonorgestrel at 12 hours' interval. This divided dose regimen can be safely simplified into a single intake of 1.5 mg levonorgestrel. This can be shown without the need for clinical trials, as serum levels of levonorgestrel are similar following a single 1.5 mg dose and following the conventional regimen of two 0.75 mg doses taken 12 hours apart (*Human Reproduction* 2002, 17(6):1472-6, herewith attached in Appendix 4). This can also be confirmed by the bioequivalence trial that can be required as part of the ANDA. The administration of one single 1.5 mg levonorgestrel tablet can thus be expected to have the same therapeutic effect as the current recommended dosage and administration of Plan B® for the approved condition of use, in other words when administered to patients as emergency contraception in the 72 hours following an act of unprotected intercourse. [1]

ENVIRONMENTAL IMPACT

The proposed action is exempt from the requirement of an environmental impact statement under 21 C.F.R. §25.31(a).

ECONOMIC IMPACT

No information is required at this time.

CERTIFICATION

HRA Pharma certifies, that, to the best of its knowledge and belief, this petition includes all information and views on which the petition relies. The petitioner knows of no data unfavorable to the petition.

Signature

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[1]Because it can be shown by bioequivalence testing that the serum levels produced by a 1.5 mg dose and two 0.75 mg doses would be essentially the same, no clinical trial is necessary to show that the 1.5 mg dose would be safe and effective. We note, however, that clinical testing has demonstrated that there were no differences in pregnancy rates or safety parameters between single and divided doses of levonorgestrel taken within 120 hours of unprotected sexual intercourse (*Lancet* 2002;360(9348):1803-10, herewith attached in Appendix 5). We also note that European authorities have concluded that it is appropriate to administer levonorgestrel emergency contraception as a single intake of 1.5 mg (labeling change granted via the European Mutual Recognition Procedure on April 30, 2003, herewith attached in Appendix 6).

APPENDIX 1

Orange Book Listing for Plan B

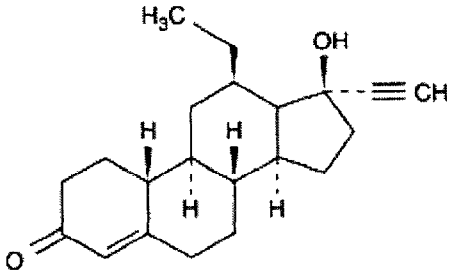
	TE Code	RLD					

APPENDIX 2
Labeling for the Listed Drug Plan B®
(source: www.go2planB.com)

Plan B® (levonorgestrel) tablets, 0.75 mg

Plan B® is intended to prevent pregnancy after known or suspected contraceptive failure or unprotected intercourse. Emergency contraceptive pills (like all oral contraceptives) do not protect against infection with HIV (the virus that causes AIDS) and other sexually transmitted diseases.

DESCRIPTION
Emergency contraceptive tablet. Each Plan B®™ 100 mg tablet contains 0.75 mg of a single active steroid ingredient, levonorgestrel [18,19-Dinorpregn-4-en-20-yn-3-one-13-ethyl-17-hydroxy-, (17a)-(-)-], a totally synthetic progestogen. The inactive ingredients present are colloidal silicon dioxide, potato starch, gelatin, magnesium stearate, talc, corn starch, and lactose monohydrate. Levonorgestrel has a molecular weight of 312.45, and the following structural and molecular formulas:



$C_{21}H_{28}O_2$

CLINICAL PHARMACOLOGY
Emergency contraceptives are not effective if the woman is already pregnant. Plan B® is believed to act as an emergency contraceptive principally by preventing ovulation or fertilization (by altering tubal transport of sperm and/or ova). In addition, it may inhibit implantation (by altering the endometrium). It is not effective once the process of implantation has begun.

Pharmacokinetics
Absorption
No specific investigation of the absolute bioavailability of Plan B® in humans has been conducted. However, literature indicates that levonorgestrel is rapidly and completely absorbed after oral administration (bioavailability about 100%) and is not subject to first pass metabolism.

After a single dose of Plan B®™ (0.75 mg) administered to 16 women under fasting conditions, maximum serum concentrations of levonorgestrel are 14.1 ± 7.7 ng/mL (mean ± SD) at an average of 1.6 ± 0.7 hours. No formal study of the effect of food on the absorption of levonorgestrel has been undertaken.

Table 1
Pharmacokinetic Parameter Values Following Single Dose Administration of Plan B®
(Levonorgestrel 0.75 mg) to Healthy Female Volunteers

	Mean (± S.D.)					
N	Cmax (ng/mL)	Tmax (h)	CL (L/h)	Vd (L)	T1/2 (h)	AUC (ng/mL/h)
16	14.1 ± 7.7	1.6 ± 0.7	7.7 ± 2.7	260.0	24.4 ± 5.3	123.1 ± 50.1

Distribution
Levonorgestrel in serum is primarily protein bound. Approximately 50% is bound to albumin and 47.5% is bound to sex hormone binding globulin (SHBG).

Metabolism
Following a single oral dosage, levonorgestrel does not appear to be extensively metabolized by the liver. The primary metabolites are 3a,5b- and 3a,5a-tetrahydrolevonorgestrel with 16b-hydroxynorgestrel also identified. Together, these account for less than 10% of parent plasma levels. Urinary metabolites hydroxylated at the 2a and 16b positions have also been identified. Small amounts of the metabolites are present in plasma as sulfate and glucuronide conjugates.

Excretion
The elimination half-life of levonorgestrel following single dose administration as Plan B®™ (0.75 mg) is 24.4 ± 5.3 hours. Excretion following single dose administration as emergency contraception is unknown, but based on chronic, low-dose contraceptive use, levonorgestrel and its metabolites are primarily excreted in the urine, with smaller amounts recovered in the feces.

Special Populations
Geriatric
This product is not intended for use in geriatric (age 65 years or older) populations and pharmacokinetic data are not available for this population.

Pediatric
This product is not intended for use in pediatric (premenarchal) populations, and pharmacokinetic data are not available for this population.

Race
No formal studies have evaluated the effect of race. However, clinical trials demonstrated a higher pregnancy rate in the Chinese population with both Plan B®™ and the Yuzpe regimen (another form of emergency contraception consisting of two doses of ethinyl estradiol 0.1 mg + levonorgestrel 0.5 mg). The reason for this apparent increase in the pregnancy rate of emergency contraceptives in Chinese women is unknown.

Hepatic Insufficiency and Renal Insufficiency
No formal studies have evaluated the effect of hepatic insufficiency or renal insufficiency on the disposition of emergency contraceptive tablets.

Drug-Drug Interactions
No formal studies of drug-drug interactions were conducted.

INDICATIONS & USAGE

Indication
Plan B®™ is an emergency contraceptive that can be used to prevent pregnancy following unprotected intercourse or a known or suspected contraceptive failure. To obtain optimal efficacy, the first tablet should be taken as soon as possible within 72 hours of intercourse. The second tablet must be taken 12 hours later.

Clinical Studies
A double-blind, controlled clinical trial in 1955 evaluable women compared the efficacy and safety of Plan B®™ (one 0.75 mg tablet of levonorgestrel taken within 72 hours of intercourse, and one tablet taken 12 hours later) to the Yuzpe regimen (two tablets of 0.25 mg levonorgestrel and 0.05 mg ethinyl estradiol, taken within 72 hours of intercourse, and two tablets taken 12 hours later). Plan B®™ was at least as effective as the Yuzpe regimen in preventing pregnancy. After a single act of intercourse, the expected pregnancy rate of 8% (with no contraception) was reduced to approximately 1% with Plan B®™. Thus, Plan B®™ reduced the expected number of pregnancies by 89%.

Emergency contraceptives are not as effective as routine contraception since their failure rate, while low based on a single use, would accumulate over time with repeated use (see Warnings). See Table 2 below.

Table 2
Percentage of Women Experiencing an Unintended Pregnancy During the First Year of Typical Use and the First Year of Perfect Use of Contraception, and the Percentage Continuing Use at the End of the first Year- United States

	% of Women Experiencing an Unintended Pregnancy within the First Year of Use		% of Women Continuing Use at One Year
Method (1)	**Typical Use[1] (2)**	**Perfect Use[2] (3)**	**(4)[3]**
Chance[4]	85	85	
Spermicide[5]	26	6	40
Periodic Abstinence	25		63
Calendar		9	
Ovulation Method		3	
Symptom-thermal[6]		2	
Post-ovulation		1	
Withdrawal	19	4	
Cap[7]			
Parous Women	40	26	42
Nulliparous Women	20	9	56
Sponge			
Parous Women	40	20	42
Nulliparous Women	20	9	56
Diaphragm[7]	20	6	56
Condom[8]			
Female (Reality)	21	5	56
Male	14	3	56
Oral Contraceptives	5		71
Progestin Only		0.5	
Combined		0.1	
IUD			
Progestin T	2.0	1.5	81
Copper T 380A	0.8	0.6	78
LNG	0.1	0.1	81
Depo-Provera	0.3	0.3	

Norplant and Norplant-2	0.05	0.05	88
Female Sterilization	0.5	0.5	100
Male Sterilization	0.15	0.10	100

Emergency Contraceptive Pills: Treatment initiated within 72 hours after unprotected intercourse reduces the risk of pregnancy by at least 75%.

Lactational Amenorrhea Method: LAM is a highly effective temporary method of contraception.[9]

1. Among typical couples who initiate use of a method (not necessarily for the first time) who experience an accidental pregnancy during the first year if they do not stop use for any other reason.
2. Among couples who initiate use of a method (not necessarily for the first time) and who use it perfectly (both consistently and correctly) the percentage who experience an accidental pregnancy during the first year if they do not stop use for any other reason.
3. Among couples attempting to avoid pregnancy, the percentage (column 4) who continue to use a method for 1 year.
4. The percent becoming pregnant in columns (2) and (3) are based on data from populations where contraception is not used and from women who cease using contraception in order to become pregnant. Among such populations, about 89% become pregnant within 1 year among women now relying on reversible methods of contraception if they abandoned contraception altogether.
5. Foams, creams, gels, vaginal suppositories, and vaginal film.
6. Cervical mucus (ovulation) method supplemented by calendar in the pre-ovulatory and basal body temperature in the post-ovulatory phase.
7. With spermicidal cream or jelly.
8. Without spermicides.
9. However, to maintain an effective protection against pregnancy, another method of contraception must be used as soon as menstruation resumes, the frequency or duration of breast feeds is reduced, bottle feeds are introduced, or the baby reaches 6 months of age.

Source: Trussell J. Contraceptive efficacy. In Hatcher RA, Trussell J, Stewart F, Cates W, Stewart GK, Guest F, Kowal D. *Contraceptive Technology; Seventeenth Revised Edition*. New York, NY: Irvington Publishers, 1998.

CONTRAINDICATIONS

Progestin-only contraceptive pills (POPs) are used as a routine method of birth control over longer periods of time, and are contraindicated in some conditions. It is not known whether these same conditions apply to the Plan B®™ regimen consisting of the emergency use of two progestin pills. POPs however, are not recommended for use in the following conditions:

- Known or suspected pregnancy
- Hypersensitivity to any component of the product
- Undiagnosed abnormal genital bleeding

WARNINGS

Plan B®™ is not recommended for routine use as a contraceptive.

Plan B®™ is not effective in terminating an existing pregnancy.

Effects on Menses

Menstrual bleeding patterns are often irregular among women using progestin-only oral contraceptives and in clinical studies of levonorgestrel for postcoital and emergency contraceptive use. Some women

may experience spotting a few days after taking Plan B®™. At the time of expected menses, approximately 75% of women using Plan B®™ had vaginal bleeding similar to their normal menses, 12-13% bled more than usual, and 12% bled less than usual. The majority of women (87%) had their next menstrual period at the expected time or within ± 7 days, while 13% had a delay of more than 7 days beyond the anticipated onset of menses. If there is a delay in the onset of menses beyond 1 week, the possibility of pregnancy should be considered.

Ectopic Pregnancy
Ectopic pregnancies account for approximately 2% of reported pregnancies (19.7 per 1000 reported pregnancies). Up to 10% of pregnancies reported in clinical studies of routine use of progestin-only contraceptives are ectopic. A history of ectopic pregnancy need not be considered a contraindication to use of this emergency contraceptive method. Health providers, however, should be alert to the possibility of an ectopic pregnancy in women who become pregnant or complain of lower abdominal pain after taking Plan B®™.

PRECAUTIONS

Pregnancy
Many studies have found no effects on fetal development associated with long-term use of contraceptive doses of oral progestins (POPs). The few studies of infant growth and development that have been conducted with POPs have not demonstrated significant adverse effects.

STD/HIV
Plan B®™, like progestin-only contraceptives, does not protect against HIV infection (AIDS) and other sexually transmitted diseases.

Physical Examination and Follow-up
A physical examination is not required prior to prescribing Plan B®™. A follow-up physical or pelvic examination, however, is recommended if there is any doubt concerning the general health or pregnancy status of any woman after taking Plan B®™.

Carbohydrate Metabolism
The effects of Plan B®™ on carbohydrate metabolism are unknown. Some users of progestin-only oral contraceptives (POPs) may experience slight deterioration in glucose tolerance, with increases in plasma insulin; however, women with diabetes mellitus who use POPs do not generally experience changes in their insulin requirements. Nonetheless, diabetic women should be monitored while taking Plan B®™.

Drug Interactions
Theoretically, the effectiveness of low-dose progestin-only pills is reduced by hepatic enzyme-inducing drugs such as the anticonvulsants phenytoin, carbamazepine, and barbiturates, and the antituberculosis drug rifampin. No significant interaction has been found with broad-spectrum antibiotics. It is not known whether the efficacy of Plan B®™ would be affected by these or any other medications.

Nursing Mothers
Small amounts of progestin pass into the breast milk in women taking progestin-only pills for long-term contraception resulting in steroid levels in infant plasma of 1-6% of the levels of maternal plasma. However, no adverse effects due to progestin-only pills have been found on breastfeeding performance, either in the quality or quantity of the milk, or on the health, growth or development of the infant.

Pediatric Use
Safety and efficacy of progestin-only pills have been established in women of reproductive age for long-term contraception. Safety and efficacy are expected to be the same for postpubertal adolescents under the age of 16 and for users 16 years and older. Use of Plan B®™ emergency contraception before menarche is not indicated.

Fertility Following Discontinuation
The limited available data indicate a rapid return of normal ovulation and fertility following discontinuation of progestin-only pills for emergency contraception and long-term contraception.

ADVERSE REACTIONS

The most common adverse events in the clinical trial for women receiving Plan B®™ included nausea (23%), abdominal pain (18%), fatigue (17%), headache (17%), and menstrual changes. The table below shows those adverse events that occurred in ³ 5% of Plan B®™ users.

Table 3
Adverse Events in Less Than or Equal to 5% of Women, by % Frequency

Most Common Adverse Events	Plan B®™ Levonorgestrel N = 977 (%)
Nausea	23.1
Abdominal pain	17.6
Fatigue	16.9
Headache	16.8
Heavier menstrual bleeding	13.8
Lighter menstrual bleeding	12.5
Dizziness	11.2
Breast tenderness	10.7
Other complaints	9.7
Vomiting	5.6
Diarrhea	5.0

Plan B®™ demonstrated a superior safety profile over the Yuzpe regimen for the following adverse events:

- *Nausea:* Occurred in 23% of women taking Plan B®™ (compared to 50% with Yuzpe)

- *Vomiting:* Occurred in 6% of women taking Plan B®™ (compared to 19% with Yuzpe)

DRUG ABUSE AND DEPENDENCE

There is no information about dependence associated with the use of Plan B®™.

OVERDOSAGE

There are no data on overdosage of Plan B®™, although the common adverse event of nausea and its associated vomiting may be anticipated.

DOSAGE AND ADMINISTRATION

One tablet of Plan B®™ should be taken orally within 72 hours after unprotected intercourse. The second tablet should be taken 12 hours after the first dose. Efficacy is better if Plan B®™ is taken as directed as soon as possible after unprotected intercourse. Plan B®™ can be used at any time during the menstrual cycle.

The user should be instructed that if she vomits within one hour of taking either dose of medication she should contact her health care professional to discuss whether to repeat that dose.

HOW SUPPLIED

Plan B®™ (levonorgestrel) tablets, 0.75 mg are available for a single course of treatment in PVC/aluminum foil blister packages of two tablets each. The tablet is white, round, and marked: INOR.

Store Plan B®™ tablets at 25°C (77°F); excursions permitted to 15 - 30°C (59 - 86°F). [See USP Controlled Room Temperature.]

Plan B®™ is distributed by the Women's Capital Corporation, 1990 M Street, NW, Suite 250 Washington, DC 20036.

Rx Only

APPENDIX 3

Proposed Labeling for the new drug ~~Norlevo 1.5~~®

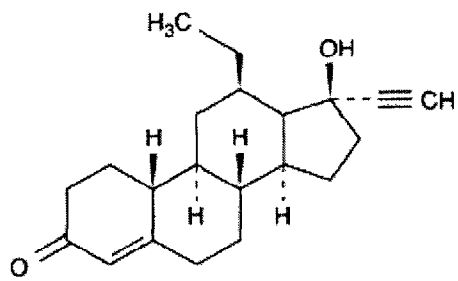
Changes to listed drug labelling highlighted

1.5 mg~~Plan B~~® (levonorgestrel) tablets, ~~0.75 mg~~

Levonorgestrel emergency contraception is ~~Plan B~~® ~~is~~ intended to prevent pregnancy after known or suspected contraceptive failure or unprotected intercourse. Emergency contraceptive pills (like all oral contraceptives) do not protect against infection with HIV (the virus that causes AIDS) and other sexually transmitted diseases.

DESCRIPTION

Emergency contraceptive tablet. Each levonorgestrel emergency contraceptive~~Plan B~~®™ ~~100~~140 mg tablet contains ~~0.75~~1.5 mg of a single active steroid ingredient, levonorgestrel [18,19-Dinorpregn-4-en-20-yn-3-one-13-ethyl-17-hydroxy-, (17a)-(-)-], a totally synthetic progestogen. The inactive ingredients present are lactose monohydrate, maize starch, povidone, anhydrous solloidal silica, and magnesium ~~stearate colloidal silicon dioxide, potato starch, gelatin, magnesium stearate, talc, corn starch, and lactose monohydrate~~. Levonorgestrel has a molecular weight of 312.45, and the following structural and molecular formulas:



$C_{21}H_{28}O_2$

CLINICAL PHARMACOLOGY

Emergency contraceptives are not effective if the woman is already pregnant. ~~Plan b~~Levonorgestrel emergency contraception® is believed to act as an emergency contraceptive principally by preventing ovulation or fertilization (by altering tubal transport of sperm and/or ova). In addition, it may inhibit implantation (by altering the endometrium). It is not effective once the process of implantation has begun.

Pharmacokinetics

Absorption

No specific investigation of the absolute bioavailability of ~~Plan~~ levonorgestrel emergency contraception~~B~~® in humans has been conducted. However, literature indicates that levonorgestrel is rapidly and completely absorbed after oral administration (bioavailability about 100%) and is not subject to first pass metabolism.

[to reflect bioequivalence trial]

~~After a single dose of Plan B®™ (0.75 mg) administered to 16 women under fasting conditions, maximum serum concentrations of levonorgestrel are 14.1 ± 7.7 ng/mL (mean ± SD) at an average of 1.6 ± 0.7 hours. No formal study of the effect of food on the absorption of levonorgestrel has been undertaken.~~

~~**Table 1**~~
~~**Pharmacokinetic Parameter Values Following Single Dose Administration of Plan b® (Levonorgestrel 0.75 mg) to Healthy Female Volunteers**~~

-	~~Mean (± S.D.)~~					
~~N~~	~~Cmax (ng/mL)~~	~~Tmax (h)~~	~~CL (L/h)~~	~~Vd (L)~~	~~T1/2 (h)~~	~~AUC (ng/mL/h)~~
~~16~~	~~14.1 ± 7.7~~	~~1.6 ± 0.7~~	~~7.7 ±~~	~~260.0~~	~~24.4 ± 5.3~~	~~123.1 ± 50.1~~

Distribution
Levonorgestrel in serum is primarily protein bound. Approximately 50% is bound to albumin and 47.5% is bound to sex hormone binding globulin (SHBG).

Metabolism
Following a single oral dosage, levonorgestrel does not appear to be extensively metabolized by the liver. The primary metabolites are 3a,5b- and 3a,5a-tetrahydrolevonorgestrel with 16b-hydroxynorgestrel also identified. Together, these account for less than 10% of parent plasma levels. Urinary metabolites hydroxylated at the 2a and 16b positions have also been identified. Small amounts of the metabolites are present in plasma as sulfate and glucuronide conjugates.

Excretion
The elimination half-life of levonorgestrel following single dose administration as ~~Plan B®™ (0.75 mg) is 24.4 ± 5.3 hours~~1.5 mg is **[to reflect bioequivalence trial]**. Excretion following single dose administration as emergency contraception is unknown, but based on chronic, low-dose contraceptive use, levonorgestrel and its metabolites are primarily excreted in the urine, with smaller amounts recovered in the feces.

Special Populations
Geriatric
This product is not intended for use in geriatric (age 65 years or older) populations and pharmacokinetic data are not available for this population.

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This product is not intended for use in pediatric (premenarchal) populations, and pharmacokinetic data are not available for this population.

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No formal studies have evaluated the effect of race. However, clinical trials demonstrated a higher pregnancy rate in the Chinese population with both ~~Plan~~ levonorgestrel emergency contraception~~B®™~~ and the Yuzpe regimen (another form of emergency contraception consisting of two doses of ethinyl estradiol 0.1 mg + levonorgestrel 0.5 mg). The reason for this apparent increase in the pregnancy rate of emergency contraceptives in Chinese women is unknown.

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No formal studies have evaluated the effect of hepatic insufficiency or renal insufficiency on the disposition of emergency contraceptive tablets.

Drug-Drug Interactions
No formal studies of drug-drug interactions were conducted.

INDICATIONS & USAGE

Indication
~~Plan~~ Levonorgestrel emergency contraception~~B®™~~ is an emergency contraceptive that can be used to prevent pregnancy following unprotected intercourse or a known or suspected contraceptive failure. To obtain optimal efficacy, the ~~first~~ levonorgestrel emergency contraception tablet should be taken as soon as possible within 72 hours of intercourse. ~~The second tablet must be taken 12 hours later.~~

Clinical Studies
A double-blind, controlled clinical trial in 1955 evaluable women compared the efficacy and safety of ~~Plan~~ levonorgestrel emergency contraception ~~B®™~~ (one 0.75 mg tablet of levonorgestrel taken within 72 hours of intercourse, and one tablet taken 12 hours later) to the Yuzpe regimen (two tablets of 0.25 mg levonorgestrel and 0.05 mg ethinyl estradiol, taken within 72 hours of intercourse, and two tablets taken 12 hours later). Levonorgestrel emergency contraception~~Plan B®™~~ was at least as effective as the Yuzpe regimen in preventing pregnancy. After a single act of intercourse, the expected pregnancy rate of 8% (with no contraception) was reduced to approximately 1% with ~~Plan~~ levonorgestrel

emergency contraception~~B®™~~. Thus, ~~Plan~~ levonorgestrel emergency contraception ~~B®™~~ reduced the expected number of pregnancies by 89%.

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Table 2
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Emergency Contraceptive Pills: Treatment initiated within 72 hours after unprotected intercourse reduces the risk of pregnancy by at least 75%.

Lactational Amenorrhea Method: LAM is a highly effective temporary method of contraception.[9]

1. Among typical couples who initiate use of a method (not necessarily for the first time) who experience an accidental pregnancy during the first year if they do not stop use for any other reason.
2. Among couples who initiate use of a method (not necessarily for the first time) and who use it perfectly (both consistently and correctly) the percentage who experience an accidental pregnancy during the first year if they do not stop use for any other reason.
3. Among couples attempting to avoid pregnancy, the percentage (column 4) who continue to use a method for 1 year.
4. The percent becoming pregnant in columns (2) and (3) are based on data from populations where contraception is not used and from women who cease using contraception in order to become pregnant. Among such populations, about 89% become pregnant within 1 year among women now relying on reversible methods of contraception if they abandoned contraception altogether.
5. Foams, creams, gels, vaginal suppositories, and vaginal film.
6. Cervical mucus (ovulation) method supplemented by calendar in the pre-ovulatory and basal body temperature in the post-ovulatory phase.
7. With spermicidal cream or jelly.
8. Without spermicides.
9. However, to maintain an effective protection against pregnancy, another method of contraception must be used as soon as menstruation resumes, the frequency or duration of breast feeds is reduced, bottle feeds are introduced, or the baby reaches 6 months of age.

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CONTRAINDICATIONS

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- Hypersensitivity to any component of the product
- Undiagnosed abnormal genital bleeding

WARNINGS

~~Plan~~ Levonorgestrel emergency contraception ~~B®™~~ **is not recommended for routine use as a contraceptive.**

~~Plan B®™~~ Levonorgestrel emergency contraception **is not effective in terminating an existing pregnancy.**

Effects on Menses

Menstrual bleeding patterns are often irregular among women using progestin-only oral contraceptives and in clinical studies of levonorgestrel for postcoital and emergency contraceptive use. Some women may experience spotting a few days after taking ~~Plan~~ levonorgestrel emergency contraception~~B®™~~. At the time of expected menses, approximately 75% of women using levonorgestrel emergency contraception (administered as two 0.75 mg doses, 12 hours apart)~~Plan B®™~~ had vaginal bleeding similar to their normal menses, 12-13% bled more than usual, and 12% bled less than usual. The majority of women (87%) had their next menstrual period at the expected time or within ± 7 days, while 13% had a delay of more than 7 days beyond the anticipated onset of menses. If there is a delay in the onset of menses beyond 1 week, the possibility of pregnancy should be considered.

Ectopic Pregnancy

Ectopic pregnancies account for approximately 2% of reported pregnancies (19.7 per 1000 reported pregnancies). Up to 10% of pregnancies reported in clinical studies of routine use of progestin-only contraceptives are ectopic. A history of ectopic pregnancy need not be considered a contraindication to use of this emergency contraceptive method. Health providers, however, should be alert to the possibility of an ectopic pregnancy in women who become pregnant or complain of lower abdominal pain after taking ~~Plan~~ levonorgestrel emergency contraception~~B®™~~.

PRECAUTIONS

Pregnancy

Many studies have found no effects on fetal development associated with long-term use of contraceptive doses of oral progestins (POPs). The few studies of infant growth and development that have been conducted with POPs have not demonstrated significant adverse effects.

STD/HIV

~~Plan~~ Levonorgestrel emergency contraception~~B®™~~, like progestin-only contraceptives, does not protect against HIV infection (AIDS) and other sexually transmitted diseases.

Physical Examination and Follow-up

A physical examination is not required prior to prescribing ~~Plan~~ levonorgestrel emergency contraception~~B®™~~. A follow-up physical or pelvic examination, however, is recommended if there is any doubt concerning the general health or pregnancy status of any woman after taking ~~Plan~~ levonorgestrel emergency contraception~~B®™~~.

Carbohydrate Metabolism

The effects of ~~Plan~~ levonorgestrel emergency contraception ~~B®™~~ on carbohydrate metabolism are unknown. Some users of progestin-only oral contraceptives (POPs) may experience slight deterioration in glucose tolerance, with increases in plasma insulin; however, women with diabetes mellitus who use POPs do not generally experience changes in their insulin requirements. Nonetheless, diabetic women should be monitored while taking ~~Plan~~ levonorgestrel emergency contraception~~B®™~~.

Drug Interactions

Theoretically, the effectiveness of low-dose progestin-only pills is reduced by hepatic enzyme-inducing drugs such as the anticonvulsants phenytoin, carbamazepine, and barbiturates, and the antituberculosis drug rifampin. No significant interaction has been found with broad-spectrum antibiotics. It is not known whether the efficacy of levonorgestrel emergency contraception~~Plan B®™~~ would be affected by these or any other medications.

Nursing Mothers
Small amounts of progestin pass into the breast milk in women taking progestin-only pills for long-term contraception resulting in steroid levels in infant plasma of 1-6% of the levels of maternal plasma. However, no adverse effects due to progestin-only pills have been found on breastfeeding performance, either in the quality or quantity of the milk, or on the health, growth or development of the infant.

Pediatric Use
Safety and efficacy of progestin-only pills have been established in women of reproductive age for long-term contraception. Safety and efficacy are expected to be the same for postpubertal adolescents under the age of 16 and for users 16 years and older. Use of ~~Plan~~ levonorgestrel B®™ emergency contraception before menarche is not indicated.

Fertility Following Discontinuation
The limited available data indicate a rapid return of normal ovulation and fertility following discontinuation of progestin-only pills for emergency contraception and long-term contraception.

ADVERSE REACTIONS

The most common adverse events in the clinical trial for women receiving ~~Plan~~ levonorgestrel emergency contraception B®™ included nausea (23%), abdominal pain (18%), fatigue (17%), headache (17%), and menstrual changes. The table below shows those adverse events that occurred in ≥ 5% of levonorgestrel emergency contraception ~~Plan~~ B®™ users.

Table 3
Adverse Events in Less Than or Equal to 5% of Women, by % Frequency

Most Common Adverse Events	~~Plan B®™~~ Levonorgestrel emergency contraception N = 977 (%)
Nausea	23.1
Abdominal pain	17.6
Fatigue	16.9
Headache	16.8
Heavier menstrual bleeding	13.8
Lighter menstrual bleeding	12.5
Dizziness	11.2
Breast tenderness	10.7
Other complaints	9.7
Vomiting	5.6
Diarrhea	5.0

Levonorgestrel emergency contraception ~~Plan B®™~~ demonstrated a superior safety profile over the Yuzpe regimen for the following adverse events:

- *Nausea:* Occurred in 23% of women taking levonorgestrel emergency contraception ~~Plan B®™~~ (compared to 50% with Yuzpe)

- *Vomiting:* Occurred in 6% of women taking levonorgestrel emergency contraception ~~Plan B®™~~ (compared to 19% with Yuzpe)

DRUG ABUSE AND DEPENDENCE

There is no information about dependence associated with the use of ~~Plan~~ levonorgestrel emergency contraception~~B~~®™.

OVERDOSAGE

There are no data on overdosage of ~~Plan~~ levonorgestrel emergency contraception~~B~~®™, although the common adverse event of nausea and its associated vomiting may be anticipated.

DOSAGE AND ADMINISTRATION

One tablet of ~~Plan~~ levonorgestrel emergency contraception~~B~~®™ should be taken orally within 72 hours after unprotected intercourse. ~~The second tablet should be taken 12 hours after the first dose.~~ Efficacy is better if ~~Plan~~ levonorgestrel emergency contraception ~~B~~®™ is taken as directed as soon as possible after unprotected intercourse. ~~Plan~~ Levonorgestrel emergency contraception ~~B~~®™ can be used at any time during the menstrual cycle.

The user should be instructed that if she vomits within one hour of taking ~~either dose of~~the medication she should contact her health care professional to discuss whether to ~~repeat that~~take another dose.

HOW SUPPLIED

~~Plan B~~®™ ~~(~~1.5 mg levonorgestrel~~)~~ tablets~~, 0.75 mg~~ are available for a single course of treatment in PVC/aluminum foil blister packages of one ~~two~~ tablets~~ each~~. The tablet is white, round, and marked: ~~INOR~~NL 1.5.

Store ~~Plan B~~1.5 mg levonorgestrel®™ tablets at 25°C (77°F); excursions permitted to 15 - 30°C (59 - 86°F). [See USP Controlled Room Temperature.]

~~Plan B~~1.5 mg levonorgestrel tablets®™ are~~is~~ distributed by ~~the Women's Capital Corporation, 1990 M Street, NW, Suite 250 Washington, DC 20036.~~ **[TBD]**.

Rx Only

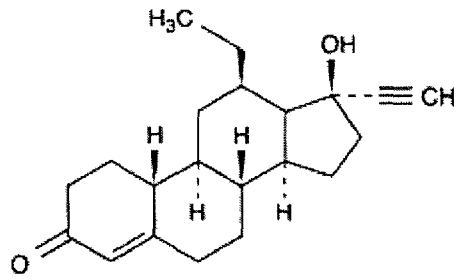
Revised label, changes to listed drug labelling incorporated

1.5 mg levonorgestrel tablets

Levonorgestrel emergency contraception is intended to prevent pregnancy after known or suspected contraceptive failure or unprotected intercourse. Emergency contraceptive pills (like all oral contraceptives) do not protect against infection with HIV (the virus that causes AIDS) and other sexually transmitted diseases.

DESCRIPTION

Emergency contraceptive tablet. Each levonorgestrel emergency contraceptive 140 mg tablet contains 1.5 mg of a single active steroid ingredient, levonorgestrel [18,19-Dinorpregn-4-en-20-yn-3-one-13-ethyl-17-hydroxy-, (17a)-(-)-], a totally synthetic progestogen. The inactive ingredients present are lactose monohydrate, maize starch, povidone, anhydrous solloidal silica, and magnesium stearate. Levonorgestrel has a molecular weight of 312.45, and the following structural and molecular formulas:



$C_{21}H_{28}O_2$

CLINICAL PHARMACOLOGY

Emergency contraceptives are not effective if the woman is already pregnant. Levonorgestrel emergency contraception is believed to act as an emergency contraceptive principally by preventing ovulation or fertilization (by altering tubal transport of sperm and/or ova). In addition, it may inhibit implantation (by altering the endometrium). It is not effective once the process of implantation has begun.

Pharmacokinetics

Absorption

No specific investigation of the absolute bioavailability of levonorgestrel emergency contraception in humans has been conducted. However, literature indicates that levonorgestrel is rapidly and completely absorbed after oral administration (bioavailability about 100%) and is not subject to first pass metabolism.

[to reflect bioequivalence trial]

Distribution

Levonorgestrel in serum is primarily protein bound. Approximately 50% is bound to albumin and 47.5% is bound to sex hormone binding globulin (SHBG).

Metabolism

Following a single oral dosage, levonorgestrel does not appear to be extensively metabolized by the liver. The primary metabolites are 3a,5b- and 3a,5a-tetrahydrolevonorgestrel with 16b-hydroxynorgestrel also identified. Together, these account for less than 10% of parent plasma levels. Urinary metabolites hydroxylated at the 2a and 16b positions have also been identified. Small amounts of the metabolites are present in plasma as sulfate and glucuronide conjugates.

Excretion

The elimination half-life of levonorgestrel following single dose administration as 1.5 mg is **[to reflect bioequivalence trial]**. Excretion following single dose administration as emergency contraception is

unknown, but based on chronic, low-dose contraceptive use, levonorgestrel and its metabolites are primarily excreted in the urine, with smaller amounts recovered in the feces.

Special Populations
Geriatric
This product is not intended for use in geriatric (age 65 years or older) populations and pharmacokinetic data are not available for this population.

Pediatric
This product is not intended for use in pediatric (premenarchal) populations, and pharmacokinetic data are not available for this population.

Race
No formal studies have evaluated the effect of race. However, clinical trials demonstrated a higher pregnancy rate in the Chinese population with both levonorgestrel emergency contraception and the Yuzpe regimen (another form of emergency contraception consisting of two doses of ethinyl estradiol 0.1 mg + levonorgestrel 0.5 mg). The reason for this apparent increase in the pregnancy rate of emergency contraceptives in Chinese women is unknown.

Hepatic Insufficiency and Renal Insufficiency
No formal studies have evaluated the effect of hepatic insufficiency or renal insufficiency on the disposition of emergency contraceptive tablets.

Drug-Drug Interactions
No formal studies of drug-drug interactions were conducted.

INDICATIONS & USAGE

Indication
Levonorgestrel emergency contraception is an emergency contraceptive that can be used to prevent pregnancy following unprotected intercourse or a known or suspected contraceptive failure. To obtain optimal efficacy, the levonorgestrel emergency contraception tablet should be taken as soon as possible within 72 hours of intercourse.

Clinical Studies
A double-blind, controlled clinical trial in 1955 evaluable women compared the efficacy and safety of levonorgestrel emergency contraception (one 0.75 mg tablet of levonorgestrel taken within 72 hours of intercourse, and one tablet taken 12 hours later) to the Yuzpe regimen (two tablets of 0.25 mg levonorgestrel and 0.05 mg ethinyl estradiol, taken within 72 hours of intercourse, and two tablets taken 12 hours later). Levonorgestrel emergency contraception was at least as effective as the Yuzpe regimen in preventing pregnancy. After a single act of intercourse, the expected pregnancy rate of 8% (with no contraception) was reduced to approximately 1% with levonorgestrel emergency contraception. Thus, levonorgestrel emergency contraception reduced the expected number of pregnancies by 89%.

Emergency contraceptives are not as effective as routine contraception since their failure rate, while low based on a single use, would accumulate over time with repeated use (see Warnings). See Table 2 below.

Table 2
Percentage of Women Experiencing an Unintended Pregnancy During the First Year of Typical Use and the First Year of Perfect Use of Contraception, and the Percentage Continuing Use at the End of the first Year- United States

	% of Women Experiencing an Unintended Pregnancy within the First Year of Use		% of Women Continuing Use at One Year
Method (1)	Typical Use[1] (2)	Perfect Use[2] (3)	(4)[3]

Chance[4]	85	85	
Spermicide[5]	26	6	40
Periodic Abstinence	25		63
Calendar		9	
Ovulation Method		3	
Symptom-thermal[6]		2	
Post-ovulation		1	
Withdrawal	19	4	
Cap[7]			
Parous Women	40	26	42
Nulliparous Women	20	9	56
Sponge			
Parous Women	40	20	42
Nulliparous Women	20	9	56
Diaphragm[7]	20	6	56
Condom[8]			
Female (Reality)	21	5	56
Male	14	3	56
Oral Contraceptives	5		71
Progestin Only		0.5	
Combined		0.1	
IUD			
Progestin T	2.0	1.5	81
Copper T 380A	0.8	0.6	78
LNG	0.1	0.1	81
Depo-Provera	0.3	0.3	
Norplant and Norplant-2	0.05	0.05	88
Female Sterilization	0.5	0.5	100
Male Sterilization	0.15	0.10	100

Emergency Contraceptive Pills: Treatment initiated within 72 hours after unprotected intercourse reduces the risk of pregnancy by at least 75%.

Lactational Amenorrhea Method: LAM is a highly effective temporary method of contraception.[9]

1. Among typical couples who initiate use of a method (not necessarily for the first time) who experience an accidental pregnancy during the first year if they do not stop use for any other reason.
2. Among couples who initiate use of a method (not necessarily for the first time) and who use it perfectly (both consistently and correctly) the percentage who experience an accidental pregnancy during the first year if they do not stop use for any other reason.
3. Among couples attempting to avoid pregnancy, the percentage (column 4) who continue to use a method for 1 year.
4. The percent becoming pregnant in columns (2) and (3) are based on data from populations where contraception is not used and from women who cease using contraception in order to become pregnant. Among such populations, about 89% become pregnant within 1 year among women now relying on reversible methods of contraception if they abandoned contraception altogether.
5. Foams, creams, gels, vaginal suppositories, and vaginal film.
6. Cervical mucus (ovulation) method supplemented by calendar in the pre-ovulatory and basal body temperature in the post-ovulatory phase.
7. With spermicidal cream or jelly.
8. Without spermicides.
9. However, to maintain an effective protection against pregnancy, another method of contraception must be used as soon as menstruation resumes, the frequency or duration of breast feeds is reduced, bottle feeds are introduced, or the baby reaches 6 months of age.

Source: Trussell J. Contraceptive efficacy. In Hatcher RA, Trussell J, Stewart F, Cates W, Stewart GK, Guest F, Kowal D. Contraceptive Technology; Seventeenth Revised Edition. New York, NY: Irvington Publishers, 1998.

CONTRAINDICATIONS

Progestin-only contraceptive pills (POPs) are used as a routine method of birth control over longer periods of time, and are contraindicated in some conditions. It is not known whether these same conditions apply to the levonorgestrel emergency contraception regimen consisting of the emergency use of a single progestin pill. POPs however, are not recommended for use in the following conditions:

- Known or suspected pregnancy
- Hypersensitivity to any component of the product
- Undiagnosed abnormal genital bleeding

WARNINGS

Levonorgestrel emergency contraception **is not recommended for routine use as a contraceptive.**

Levonorgestrel emergency contraception **is not effective in terminating an existing pregnancy.**

Effects on Menses

Menstrual bleeding patterns are often irregular among women using progestin-only oral contraceptives and in clinical studies of levonorgestrel for postcoital and emergency contraceptive use. Some women may experience spotting a few days after taking levonorgestrel emergency contraception. At the time of expected menses, approximately 75% of women using levonorgestrel emergency contraception (administered as two 0.75 mg doses, 12 hours apart) had vaginal bleeding similar to their normal menses, 12-13% bled more than usual, and 12% bled less than usual. The majority of women (87%) had their next menstrual period at the expected time or within ± 7 days, while 13% had a delay of more than 7 days beyond the anticipated onset of menses. If there is a delay in the onset of menses beyond 1 week, the possibility of pregnancy should be considered.

Ectopic Pregnancy
Ectopic pregnancies account for approximately 2% of reported pregnancies (19.7 per 1000 reported pregnancies). Up to 10% of pregnancies reported in clinical studies of routine use of progestin-only contraceptives are ectopic. A history of ectopic pregnancy need not be considered a contraindication to use of this emergency contraceptive method. Health providers, however, should be alert to the possibility of an ectopic pregnancy in women who become pregnant or complain of lower abdominal pain after taking levonorgestrel emergency contraception.

PRECAUTIONS

Pregnancy
Many studies have found no effects on fetal development associated with long-term use of contraceptive doses of oral progestins (POPs). The few studies of infant growth and development that have been conducted with POPs have not demonstrated significant adverse effects.

STD/HIV
Levonorgestrel emergency contraception, like progestin-only contraceptives, does not protect against HIV infection (AIDS) and other sexually transmitted diseases.

Physical Examination and Follow-up
A physical examination is not required prior to prescribing levonorgestrel emergency contraception. A follow-up physical or pelvic examination, however, is recommended if there is any doubt concerning the general health or pregnancy status of any woman after taking levonorgestrel emergency contraception.

Carbohydrate Metabolism
The effects of levonorgestrel emergency contraception on carbohydrate metabolism are unknown. Some users of progestin-only oral contraceptives (POPs) may experience slight deterioration in glucose tolerance, with increases in plasma insulin; however, women with diabetes mellitus who use POPs do not generally experience changes in their insulin requirements. Nonetheless, diabetic women should be monitored while taking levonorgestrel emergency contraception.

Drug Interactions
Theoretically, the effectiveness of low-dose progestin-only pills is reduced by hepatic enzyme-inducing drugs such as the anticonvulsants phenytoin, carbamazepine, and barbiturates, and the antituberculosis drug rifampin. No significant interaction has been found with broad-spectrum antibiotics. It is not known whether the efficacy of levonorgestrel emergency contraception would be affected by these or any other medications.

Nursing Mothers
Small amounts of progestin pass into the breast milk in women taking progestin-only pills for long-term contraception resulting in steroid levels in infant plasma of 1-6% of the levels of maternal plasma. However, no adverse effects due to progestin-only pills have been found on breastfeeding performance, either in the quality or quantity of the milk, or on the health, growth or development of the infant.

Pediatric Use
Safety and efficacy of progestin-only pills have been established in women of reproductive age for long-term contraception. Safety and efficacy are expected to be the same for postpubertal adolescents under the age of 16 and for users 16 years and older. Use of levonorgestrel emergency contraception before menarche is not indicated.

Fertility Following Discontinuation
The limited available data indicate a rapid return of normal ovulation and fertility following discontinuation of progestin-only pills for emergency contraception and long-term contraception.

ADVERSE REACTIONS

The most common adverse events in the clinical trial for women receiving levonorgestrel emergency

menstrual changes. The table below shows those adverse events that occurred in ³ 5% of levonorgestrel emergency contraception users.

Table 3
Adverse Events in Less Than or Equal to 5% of Women, by % Frequency

Most Common Adverse Events	Levonorgestrel emergency contraception N = 977 (%)
Nausea	23.1
Abdominal pain	17.6
Fatigue	16.9
Headache	16.8
Heavier menstrual bleeding	13.8
Lighter menstrual bleeding	12.5
Dizziness	11.2
Breast tenderness	10.7
Other complaints	9.7
Vomiting	5.6
Diarrhea	5.0

Levonorgestrel emergency contraception demonstrated a superior safety profile over the Yuzpe regimen for the following adverse events:

- *Nausea:* Occurred in 23% of women taking levonorgestrel emergency contraception (compared to 50% with Yuzpe)

- *Vomiting:* Occurred in 6% of women taking levonorgestrel emergency contraception (compared to 19% with Yuzpe)

DRUG ABUSE AND DEPENDENCE

There is no information about dependence associated with the use of levonorgestrel emergency contraception.

OVERDOSAGE

There are no data on overdosage of levonorgestrel emergency contraception, although the common adverse event of nausea and its associated vomiting may be anticipated.

DOSAGE AND ADMINISTRATION

One tablet of levonorgestrel emergency contraception should be taken orally within 72 hours after unprotected intercourse. Efficacy is better if levonorgestrel emergency contraception is taken as directed as soon as possible after unprotected intercourse. Levonorgestrel emergency contraception can be used at any time during the menstrual cycle.

The user should be instructed that if she vomits within one hour of taking the medication she should contact her health care professional to discuss whether to take another dose.

HOW SUPPLIED

1.5 mg levonorgestrel tablets are available for a single course of treatment in PVC/aluminum foil blister packages of one tablet each. The tablet is white, round, and marked: NL 1.5.

Store 1.5 mg levonorgestrel tablets at 25°C (77°F); excursions permitted to 15 - 30°C (59 - 86°F). [See USP Controlled Room Temperature.]

1.5 mg levonorgestrel tablets are distributed by **[TBD]**.

Rx Only

APPENDIX 4

Human Reproduction 2002, 17(6):1472-6

Human Reproduction Vol.17, No.6 pp. 1472–1476, 2002

Pharmacokinetic study of different dosing regimens of levonorgestrel for emergency contraception in healthy women

Elof Johansson[1], Vivian Brache[2,6], Frank Alvarez[2], Anibal Faundes[2,3], Leila Cochon[2], Sirpa Ranta[4], Mark Lovern[5] and Narender Kumar[1]

[1]Center for Biomedical Research, The Population Council, New York, NY, USA, [2]PROFAMILIA, Santo Domingo, Dominican Republic, [3]CEMICAMP, Campinas, SP, Brasil, [4]Steroid Research Laboratory, Institute of Biomedicine, University of Helsinki, Helsinki, Finland and [5]Pharsight Corporation, Cary, NC, USA

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BACKGROUND: Levonorgestrel (LNG) is a commonly used progestin for emergency contraception; however, litt is known about its pharmacokinetics and optimal dose for use. METHODS: Serum levels of LNG and sex hormon binding globulin (SHBG) were measured in five women who received three different regimens: A: 0.75 mg LN twice with a 12 h interval; B: 0.75 mg twice with a 24 h interval; and C: 1.50 mg in a single dose, with a washo period of 28 days between each treatment. Blood samples were taken before pill intake and at 1, 2, 4, 8 and 12 after each dose, every 12 h up to day 4 and every 24 h until day 10. LNG and SHBG were measured in all sample RESULTS: Maximum LNG concentrations were of ~27 nmol/l for treatments A and B, and close to 40 nmol/l fo treatment C. The area under the curve was significantly higher for treatment C during the first 12 h, an significantly lower for treatment B during the first 24 h. After 48 h and up to 9 days from onset of treatmen serum LNG levels were similar in all three regimens. SHBG levels remained stable for 24 h, decreasing to 60% c the initial value from day 5 until day 10, with no difference between regimens. CONCLUSIONS: The similarity c LNG serum levels obtained with one single dose of 1.5 mg or two doses of 0.75 mg with a 12 h interval justify clinical comparison of these two regimes.

Key words: emergency contraception/levonorgestrel/pharmacokinetics/SHBG

Introduction

Emergency contraception (EC) is a woman's only reliable option for preventing pregnancy after unprotected sexual intercourse or contraceptive method failure. Although EC has been available for >20 years, it has been an underused modality among contraceptive methods. In recent years, it has regained relevance in the field of reproductive health, with the growing realization that EC could save millions of women (and health care money) from experiencing unplanned or unwanted pregnancies (Berer *et al.*, 1995).

Although use of levonorgestrel (LNG) for EC is increasing, the knowledge of the pharmacokinetics of LNG when used for EC and the selection of the dose currently recommended is based on limited data. In the early 1970s, pioneering studies explored various doses (0.15, 0.25 and 0.4 mg) of LNG-only for post-coital contraception (Larranaga, 1971; Kesseru *et al.*, 1974). Later studies evaluated the post-coital use of 0.75 mg of LNG (Seregely, 1982; Bhattacharjee *et al.*, 1987) with a different concept of multiple use per cycle after each act of unprotected coitus. This concept was not pursued due to frequent cycle disruption and bleeding irregularities, as wel as lower effectiveness than achieved with the combined pi (Larranaga, 1971; Kesseru *et al.*, 1974; Seregely, 1982; Worl Health Organization, 1987).

A randomized comparative study of EC using the LN (0.75 mg for two doses, 12 h apart) and Yuzpe regimes (tw doses of 100 μg of ethinyl estradiol and 0.5 mg LNG, 12 apart) showed equal effectiveness at 2.4 and 2.6% respectivel (Ho and Kwan, 1993). However, fewer side-effects wer observed among users of the LNG-only regimen. A larg multicentre study reported higher efficacy and reaffirmed lower incidence of side-effects with the LNG regimen (tw doses of 0.75 mg, 12 h apart), compared with the Yuzpe metho (World Health Organization, 1998). Based on this study, th LNG regimen would be the method of choice.

An inconvenience of the current LNG regimen is the require 12 h interval, which may be cumbersome for some women This schedule of use was selected without a properly designe schedule-finding study; therefore, it is not known whether th same protection may be achieved with a 24 h interval betwee

doses or with both pills taken together. Furthermore, there are no data available on the pharmacokinetics associated with the current recommended mode of administration of LNG for EC. Four studies have investigated different doses and regimens of LNG for EC: three studies involving a single administration of 0.75 mg LNG (Shi *et al.*, 1988; Landgren *et al.*, 1989; He *et al.*, 1990) and one using a single dose of 1.0 mg LNG (Weiner *et al.*, 1976a). These studies have demonstrated that LNG has a long half-life, which could be explained by the high affinity of LNG for sex hormone-binding globulin (SHBG) (Victor *et al.*, 1976).

The objective of this study was to describe the pharmacokinetics of the currently accepted LNG EC regimen consisting of two doses of 0.75 mg LNG (Norlevo®; HRA Pharma, Paris, France) given 12 h apart (treatment A), as well as the pharmacokinetics associated with two additional regimens: two doses of 0.75 mg LNG given 24 h apart (treatment B), and a single dose of 1.5 mg LNG (two 0.75 mg tablets; treatment C).

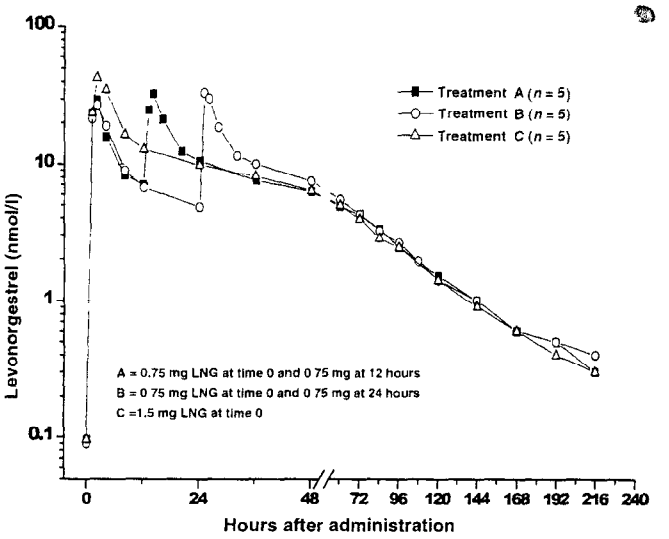

Figure 1. Mean levonorgestrel (LNG) serum levels in women following oral administration of three different regimes of LNG for emergency contraception.

Materials and methods

Subjects

A total of five non-breastfeeding healthy women, attending the Reproductive Health Clinic at PROFAMILIA, Dominican Republic, were enrolled in the study. All participants read and signed a written informed consent before enrolment in the study. The inclusion criteria were: 18–45 years of age; haemoglobin levels >11 g/dl; body weight 55–80 kg, protection against pregnancy by use of barrier methods, abstinence or surgical sterilization; no use of hormonal contraceptives in the month before enrolment or of injectable contraceptives 4 months prior to enrolment; and normal liver function. Each subject included in the study was assessed by a medical history, a complete general and physical examination and determination of eligibility through pre-admission screening. Each subject provided a blood sample before the initiation of the study for haemoglobin measurement and for the standard assessment of liver function: bilirubin, alanine aminotransferase (ALT or SGPT), aspartate aminotransferase (AST or SGOT), alkaline phosphatase and albumin.

Design of the study

Each woman participated in the three arms of the study with a washout period between treatments of 27–28 days. The treatments were, A: two doses of 0.75 mg LNG given 12 h apart; treatment B: two doses of 0.75 mg LNG given 24 h apart; and treatment C: a single dose of 1.5 mg LNG (two 0.75 mg tablets).

Blood samples were taken just before pill intake and then serially at 1, 2, 4, 8 and 12 h after each dose; samples were then taken every 12 h on days 2, 3 and 4, and every 24 h on days 5, 6, 7, 8, 9 and 10. Clinical staff provided the LNG tablets at the time of intake. Subjects remained at the clinic for 12 h following each dose.

Assays

LNG and SHBG were assayed at the Steroid Research Laboratory, Helsinki, Finland. LNG was measured by a conventional radioimmunoassay as previously described (Weiner *et al.*, 1976b). The steroid was extracted with diethyl ether and then measured by radioimmunoassay with a specific antibody and tritium-labelled LNG as a tracer, obtained from Schering AG (Berlin, Germany). The precision of the assay was evaluated by determining the intra- and inter-assay coefficients of variation (CV) in the optimal range of assay. The intra- and inter-assay CVs were 5.6–9.9% and 8.0–11.0% respectively. With the purpose of avoiding inter-assay bias, all samples of each subject (three arms) were analysed in the same radioimmunoassay run.

The concentration of SHBG in the sera was measured by a time-resolved fluoroimmunoassay, using a commercial kit (DELFIA) manufactured by Wallac Finland Oy, Turku, Finland. According to the manufacturer, the intra- and inter-assay CVs were 1.3–1.8% and 5.1–10.1% respectively. Free LNG index was calculated as the ratio between serum LNG (nmol/l) and SHBG (nmol/l) at 12, 24 and 24 h thereafter until day 9.

Comparison of pharmacokinetic parameters

Each individual concentration–time curve was fitted according to a two-compartment model using WIN NONLIN software (Pharsight Corporation, Cary, NC, USA). All treatments were compared in a single pharmacokinetic analysis. The area under the concentration–time curve, maximal concentration (Cmax), time to reach maximal concentration (Tmax) and biological half-life were obtained from software-calculated values for each treatment. Pharmacokinetic parameters are shown as geometric means with 95% confidence intervals and were compared using one-way analysis of variance (ANOVA).

Results

The weight range of the five participating women was 59–77 kg (mean ± SD: 67.6 ± 6.6). Mean serum LNG concentrations following the various treatments are shown in Figure 1. The pharmacokinetic parameters obtained following WIN NONLIN analysis are shown in Tables I and II. The LNG Cmax after treatment C was ~50% higher than the Cmax obtained after treatments A and B (P = 0.03). Maximum serum concentrations of LNG were reached between 1.5 and 1.8 h after the administration of 0.75 mg and 2.6 h after the administration of 1.5 mg of LNG (Table I). The peak observed following the second dose, 12 or 24 h later, was slightly higher than the initial peak (32.8 versus 29.5 nmol/l and 30.0 versus 27.2 nmol/l respectively). By 48 h all three treatment arms had very similar LNG levels (A = 6.2, B = 7.4 and C = 6.3 nmol/l; Figure 1). It is interesting that due to the long biological half-life of LNG, serum LNG levels >1.3 nmol/l were

Table I. Geometric mean and 95% confidence interval (CI) of pharmacokinetic parameters of LNG in women

Tx	No of subjects	Cmax (nmol/l)	Tmax (h)	Terminal half-life (h)	AUC (0–12 h) (nmol/l)	AUC (0–24 h) (nmol/h)	AUC (total) (nmol/h)
A	5	25.3	1 8	43.7	158.6	358 5	443.6
	95% CI	16 2–39 8	1.4–2.4	23 4–81.3	117 5–213 8	251 2–512 9	323.6–616.6
B	5	26.8	1.4	32.0	164.9	232 8[c]	432.5
	95% CI	20.0–35 5	1.0–2.1	25 1–40.7	125 9–218.8	177.8–309 0	354.8–524 8
C	5	39 3[a]	2.5[a]	43 3	282 4[b]	415 9	925 0[b]
	95% CI	33 9–45 7	1 8–3.6	38.9–47.9	257.0–309.0	346.7–501.2	676.1–1258 9

Comparison between treatments using one-way ANOVA. [a]$P < 0.04$, [b]$P < 0.001$, [c]$P < 0.007$.
Cmax = peak serum concentration, Tmax = time to peak serum concentration; AUC = area under the concentration–time curve.

Table II. Pharmacokinetic parameters of LNG in women treated with LNG for emergency contraception (individual values)

Treatment	Subject no	Cmax (nmol/l)	Tmax (h)	Terminal half-life (h)	AUC (nmol/l/h) 0–12 h	AUC (nmol/l/h) 0–24 h	AUC (nmol/l/h) Total
A	3001	42 89	1.3	35.6	208	493	534.3
	3002	17.71	2.2	89.6	119	244	333.9
	3003	18.55	2.2	48 7	130	296	393.8
	3004	25.66	1 5	23	166	378	387.7
	3005	28 56	2.0	44.8	188	440	630.8
B	3001	36 263	1 5	36 6	232	323	524 8
	3002	28.316	1 3	32.1	156	207	406.7
	3003	22.532	1.7	24 6	149	215	436.5
	3004	20 259	2.0	28.9	127	183	344.5
	3005	29.271	0 9	40.5	178	260	471.3
C	3001	40.85	2.8	47 5	300	437	975.9
	3002	46.43	1.6	43 0	252	342	726.1
	3003	39 56	2.5	42.3	276	374	703.2
	3004	38 11	2.7	38.3	300	484	1121.0
	3005	32 85	3.4	46.0	287	460	1212.1

Cmax = peak serum concentration, Tmax = time to peak serum concentration; AUC = area under the concentration–time curve.

observed 5 days after administration of the first dose, and levels near 0.6 nmol/l were present 1 week post-administration, with no discernible difference between the three regimens from days 3–9 after initiation of treatment.

The area under the curve (AUC) calculated for the first 12 h after LNG administration was very similar for treatments A and B and significantly higher for treatment C ($P = 0.00014$; Table I). The AUC for the 24 h period was lowest for treatment B ($P = 0.0067$), while there were no significant differences between treatments A and C (Table I). The total AUC (including 9 days of observation) for treatment C was significantly higher than for treatments A and B ($P = 0.0003$; Table I).

SHBG (mean ± SD) levels were 51.2 ± 21.7, 53.0 ± 15.1 and 53.4 ± 11.3 nmol/l, just before the administration of treatments A, B and C respectively. SHBG serum levels remained essentially unchanged during the first 24 h after drug intake (Figure 2). The first decrease was noted in the 48 h sample (~10%), followed by a continuous, regular decrease down to ~60% of baseline values at day 5 post-initiation of treatment. SHBG remained depressed at the same level through to day 9 after initiation of treatment, with no difference between the three regimens (Figure 2). There was a good correlation between baseline SHBG levels and LNG concentrations (Cmax) for treatments A and B ($r = 0.79$ and 0.86 respectively), but not for treatment C ($r = 0.387$) which corresponded to the highest dose and LNG serum levels. There was no correlation between body mass index of the five subjects and LNG levels (Cmax) achieved with any of the three regimes.

The free LNG index curve followed a similar pattern as the LNG concentration curve, with higher levels for treatment C at 12 h and for treatment A at 24 h. The peak after the second dose with treatment B was missed, because SHBG was not measured in the 36 h sample. No differences between regimes were observed from 48 h to day 9 after treatment.

Adverse events were reported within 72 h after intake by one woman during treatment A, by two using treatment B and by one during use of treatment C. The reported side effects were nausea (three women), sleepiness (two women) and headache (one woman). No subject reported vomiting.

Discussion

The main purpose of this study was to compare the standard EC LNG regime with two alternative schedules: increasing the interval to 24 h between doses or a single administration of the total dose. The results of this study showed that the AUC after administration of one single dose of 1.5 mg was greater than after two doses of 0.75 mg with a 12 or 24 h interval between doses.

The pharmacokinetic parameters observed in this study, with the administration of 0.75 mg of LNG, fit within those reported in China by Shi *et al.* and also by He *et al.* after administration of Postinor (He *et al.*, 1990; Shi *et al.*, 1998). On the other hand,

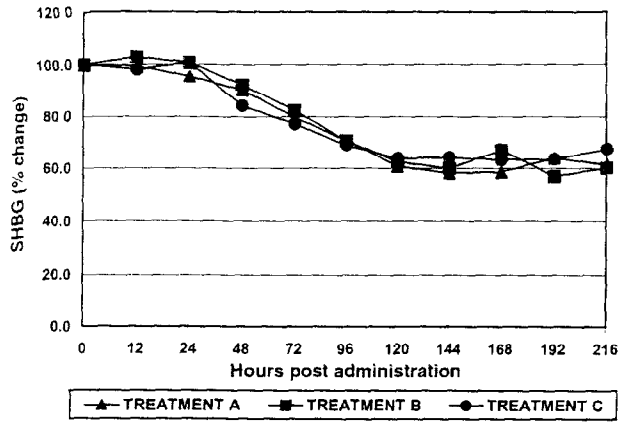

Figure 2. Serum SHBG levels (expressed as percentage of baseline) in women following oral administration of three different regimes of LNG for emergency contraception. Treatments A (0.75 mg twice with 12 h interval), B (0.75 mg twice with 24 h interval) and C (single administration of 1.5 mg).

Landgren *et al.* found peak LNG concentrations much lower than ours (16 nmol/l versus 29 or 27 nmol/l, at 2 h after administration) (Landgren *et al.*, 1989). In addition, these last authors found that LNG levels were undetectable 72 h after one single administration, while we found mean levels of 0.6 pmol/l 1 week after two successive doses with 12 or 24 h intervals. Pharmacokinetic studies of the Chinese-manufactured pill of 0.75 mg (He *et al.*, 1990) showed lower concentrations of LNG and a delay in reaching peak levels. While the Tmax observed with European-manufactured pills ranged between 1.5–2.0 h, the Tmax observed with the Chinese pill ranged between 3–4 h. The authors attributed these differences to the lesser degree of micronization of LNG in the Chinese formulation (He *et al.*, 1990).

The comparison of the data from all these studies underlines the importance of repeating these analyses in different settings, given the variability between sites, subjects and formulations.

SHBG did not seem to influence LNG serum levels during the initial 2 days after treatment, since SHBG was unchanged during the first 48 h after initiation of treatment. The decrease in SHBG was observed at a time when the expected contraceptive effect already should have occurred.

An earlier study on the effect of the Yuzpe regime upon ovarian function (Croxatto *et al.*, 2002) showed that the effect of hormone administration on gonadotrophin levels was already observed 24 h after the first dose. Therefore, there are good reasons to believe that the bioavailability of LNG during the first 12 h after administration is critical to achieve the expected effect on ovulatory function and, possibly, a local effect on sperm penetration. If this is the case, the administration of a single larger dose would be more effective than the same amount of LNG divided into two doses administered 12 h apart.

We do not know, however, if there is a real need for such high LNG plasma levels as those observed after administration of the 1.5 mg dose (~40 nmol/l). It may well be that a single dose of 0.75 mg would be sufficient to achieve maximal biological effect, and there would be no advantage with the administration of a higher dose. In fact, earlier reports suggest that even a lower single dose, 0.4 mg of LNG, could be sufficient to cause the desired contraceptive effect (Kesseru *et al.*, 1974). Furthermore, in a comparative study of Postinor and the Chinese-manufactured pill with 0.75 mg of LNG, the same clinical effectiveness with both formulations was observed, in spite of considerably lower LNG serum levels attained with the Chinese formulation (Cmax 18.9 nmol/l) than after the administration of Postinor (Cmax 33.9 nmol/l) (He *et al.*, 1990). In addition, when Norplant® contraceptive implants were inserted during the advanced follicular phase (days 8–13), ovulation inhibition was achieved in 60% of users in the first cycle of use, even though peak levels reached only 3 nmol/l at 24–72 h post-insertion. This level is well below the peak LNG concentrations observed with the three regimens described above (Brache *et al.*, 1999).

There are obvious practical advantages of administering a single dose over two doses given 12 h apart; a single dose would improve compliance and eliminate the need to disrupt sleep for drug intake. A possible disadvantage of the higher single dose could be greater intolerance with more side-effects, including the possibility of vomiting. In this small sample no evidence of greater intolerance and no episodes of vomiting were observed.

On the other hand, administration of the second dose 24 h after the first one (treatment B) was associated with a lower AUC during the first 24 h, as should be expected. It is doubtful that the rise in plasma level after the second administration, 24 h later, would make a significant contribution to the mechanism of action of EC. Thus, although the 24 h interval is programmatically convenient, it may not offer advantages over one single administration of 0.75 mg of LNG.

The overall results of this study suggest that the clinical comparison of the standard LNG regimen with single administration of the entire dose is fully justified. In addition, it is worth considering a single dose of 0.75 mg as a potentially equally effective alternative to the standard LNG regimen. Moreover, the effects of lower doses of LNG on gonadotrophin levels and the ovulatory process should be explored, in order to identify the minimal dose of LNG that could be effective as EC.

Acknowledgement

The authors gratefully acknowledge Ms Margaret Small for editorial assistance.

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Submitted on November 1, 2001, accepted on February 12, 2002

APPENDIX 5

Lancet 2002;360(9348):1803-10

Articles

Low dose mifepristone and two regimens of levonorgestrel for emergency contraception: a WHO multicentre randomised trial

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Summary

Background A single 10 mg dose of mifepristone, and two 0·75 mg doses of levonorgestrel 12 h apart, are effective for emergency contraception. Because no studies had compared the efficacies of both compounds, or investigated a single dose of 1·5 mg levonorgestrel, we undertook this three-arm trial.

Methods We did a randomised, double-blind trial in 15 family-planning clinics in 10 countries. We randomly assigned 4136 healthy women with regular menstrual cycles, who requested emergency contraception within 120 h of one unprotected coitus, to one of three regimens: 10 mg single-dose mifepristone; 1·5 mg single-dose levonorgestrel; or two doses of 0·75 mg levonorgestrel given 12 h apart. The primary outcome was unintended pregnancy; other outcomes were side-effects and timing of next menstruation. Analysis was by intention to treat, but we did exclude some patients from the final analyses.

Findings Of 4071 women with known outcome, pregnancy rates were 1·5% (21/1359) in those given mifepristone, 1·5% (20/1356) in those assigned single-dose levonorgestrel, and 1·8% (24/1356) in women assigned two-dose levonorgestrel. These proportions did not differ significantly (p=0·83). The relative risk of pregnancy for single-dose levonorgestrel compared with two-dose levonorgestrel was 0·83 (95% CI 0·46–1·50), and that for levonorgestrel (the two regimens combined) compared with mifepristone, 1·05 (0·63–1·76). Side-effects were mild and did not differ greatly between groups, and most women menstruated within 2 days of the expected date. Women who took levonorgestrel had earlier menses than did those who took mifepristone.

Interpretation The three regimens studied are very efficacious for emergency contraception and prevent a high proportion of pregnancies if taken within 5 days of unprotected coitus. Mifepristone and levonorgestrel do not differ in efficacy. A 1·5 mg single levonorgestrel dose can substitute two 0·75 mg doses 12 h apart.

Lancet 2002; **360:** 1803–10

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Introduction

Two 0·75 mg doses of levonorgestrel administered 12 h apart, taken up to 72 h after unprotected intercourse is better tolerated and more efficacious than the standard in hormonal emergency contraception—ie, the Yuzpe regimen (two doses of 0·1 mg ethinyloestradiol, 0·5 mg levonorgestrel, 12 h apart).[1] Results from a systematic review[2] that combined these data with those from another trial, in which treatment was administered up to 48 h after unprotected intercourse,[3] confirmed these conclusions. The two-dose regimen of levonorgestrel has been approved in more than 80 countries and is progressively replacing the Yuzpe regimen.

A comparison of three single doses of mifepristone (600 mg, 50 mg, and 10 mg) administered up to 120 h after intercourse for emergency contraception showed that the proportions of pregnancies (1·3%, 1·1%, and 1·2%, respectively) did not differ between these three doses.[4] The investigators concluded that a 60-fold reduction in the dose of mifepristone did not seem to decrease its effectiveness as an emergency contraceptive. No major side-effects occurred in any participants of that trial; however, the delay in the onset of next menstruation was significantly related to the mifepristone dose (p<0·01). A systematic review[2] combined results of trials that compared high doses of mifepristone (>50 mg) with low doses (≤10mg), or that compared mid-range doses (25–50 mg) with low doses (≤10 mg) and reported no

evidence of a dose-related efficacy. However, the side-effect profile was better with low doses than with mid or high doses. These results suggest that mifepristone could improve existing emergency contraception options, because it can be administered in a single low dose with few side-effects. If levonorgestrel could also be given as a single dose, treatment would be simplified and compliance and patients' acceptance of the drug could be increased.

Our aim in this randomised, double-blind, multinational trial was, therefore, to compare the efficacy and side-effects of three treatments, when administered up to 120 h (5 days) after unprotected coitus: a single dose of 10 mg mifepristone; a single dose of 1·5 mg levonorgestrel; and two separate doses of 0·75 mg levonorgestrel given 12 h apart . The main outcomes were pregnancy rates, proportions of pregnancies prevented, side-effects and timing of the first menstrual period after treatment. We also planned to analyse the effect of treatment delay on efficacy.

Methods

Patients

This trial was done in 15 family-planning clinics in China, Finland, Georgia, Hungary, India, Mongolia, Slovenia, Sweden, Switzerland, and the UK (table 1).

We asked women presenting for emergency contraception to participate, and included those who were healthy, had regular menstrual cycles (24–42 days' duration), and who requested emergency contraception within 120 h of a single act of unprotected coitus in the present menstrual cycle. Participants also had to be willing to abstain from unprotected intercourse during that cycle, and be available for follow-up over the next 6 weeks. Women who had recently discontinued hormonal contraception or had been pregnant were included only if they had had at least one complete and normal menstrual cycle before the current cycle. Furthermore, the results of a sensitive pregnancy test (25 IU human chorionic gonadotropin) taken at admission had to be negative. We excluded women who were pregnant, breastfeeding, using hormonal contraception in the current cycle, using the rhythm method of natural family planning in the same cycle, uncertain about the date of the most recent menses, and those with contraindications for mifepristone use (chronic adrenal failure, a known allergy to mifepristone, severe asthma not controlled by corticosteroid therapy, or inherited porphyria). In addition, the centres did not enrol women likely to continue a pregnancy should emergency contraception fail. Relevant medical, gynaecological, and obstetric histories were recorded, as was the date of last menstruation, the expected date of next menses, and the date and clock time of unprotected intercourse.

All participants gave written informed consent. Institutional review boards at each of the participating centres and WHO Secretariat Committee on Research Involving Human Subjects gave ethics approval.

Randomisation

We used a computer-generated randomisation sequence developed by WHO to assign participants in each centre to one of three treatment groups: single-dose mifepristone; single-dose levonorgestrel; or two-dose levonorgestrel. Each centre received assignments by randomly-permuted blocks with a fixed block size of 10.

Allocation was concealed by the use of sealed, sequentially-numbered treatment packs, which were filled and labelled in accordance with the list of randomisation for each centre by Labatec, Geneva, Switzerland. Before and during the trial, we tested samples of the packed drugs to ensure the quality of supplies being sent to participating centres. The results confirmed correct labelling and drug content of the tablets.

In the 10 mg mifepristone group, women received two 5 mg tablets of mifepristone and two placebo tablets identical in appearance to levonorgestrel; in the single-dose levonorgestrel group, women were given two 0·75 mg levonorgestrel tablets and two placebo tablets identical in appearance to mifepristone; and in the two-dose levonorgestrel group women received one 0·75 mg levonorgestrel tablet, one placebo tablet identical in appearance to levonorgestrel, and two placebo tablets identical in appearance to mifepristone. The second dose comprised one dummy levonorgestrel tablet in the first two groups and one 0·75 mg levonorgestrel tablet in the third group. Mifepristone tablets and mifepristone placebo were provided by Roussel-Uclaf, Romainville, France, and levonorgestrel tablets and levonorgestrel placebo were provided by Gedeon Richter Ltd, Budapest, Hungary.The first dose was taken at the clinic, and the second was taken 12 h later at home.

Outcome measures

The primary outcome measure was unintended pregnancy, confirmed by a positive pregnancy test, or by vaginal ultrasound at follow-up, or both. We considered crude and adjusted pregnancy rates as well as the estimated reduction in expected pregnancies, or prevented fraction (1 minus [observed pregnancies/expected pregnancies]). We estimated the expected number of pregnancies in each group by multiplying the number of women having unprotected intercourse on each day of the menstrual cycle by the probability of conception on that cycle day. We estimated the date of ovulation by subtracting 14 days from the expected date of onset of the next menstrual period. We used estimated conception probabilities by cycle day from two data sets created by Trussell and colleagues,[5] which include only clinical pregnancies and exclude those diagnosed by biochemistry only (pooled-recognisable). Other outcome measures were side-effects in the week after the start of treatment and the timing of the first menstruation after treatment—ie, the difference between estimated and actual dates of menses onset.

Procedures

Women were advised not to have unprotected sex, and were given condoms. We asked participants to keep a diary of side-effects in the week after the treatment, and to record spotting or bleeding, acts of intercourse, and whether a condom was used, until the next menses or the follow-up visit, whichever came first. No incentives were given, and the trial drugs were supplied free of charge to participants.

A follow-up visit was arranged about 1 week after the estimated onset of the next menstrual bleeding, and the date of the visit was written on the diary card. If the woman had normal menstruation, she had completed the trial. If menstruation was not normal, or had not started by the time of the follow-up visit, we did a pregnancy test. For women with a negative test result, we arranged another follow-up appointment; however, if the test was positive, we did an ultrasound examination to estimate the duration of gestation. If menses had not occurred by the time of the second follow-up visit and the pregnancy test was negative, treatment was regarded as successful. WHO provided the centres with pregnancy tests and condoms.

Clinicians, participants, and investigators were unaware of drug assignments and this double-blinding was maintained until after the final analysis; only the person who prepared the random lists had access to them.

Principal investigators met before the trial to review the protocol and ensure uniform criteria for the assessment of outcomes. While the trial was in progress, the trial coordinator and other WHO staff visited trial sites. Principal investigators also monitored the trial, and all but one of the centres had previously participated in previous multicentre trials of emergency contraception. This trial was not monitored by an external independent committee, because the drugs used are already registered and available for widespread use. Data quality monitoring was done in accordance with the standard operating procedures presently used in WHO, Geneva.

Statistical analysis

The proposed sample size for this trial was 4200 women, with 1400 women per treatment group. This sample size was chosen to detect a minimum difference between a 1·2% failure rate in women treated with mifepristone[4] and a 2·9% failure rate[3] in women treated with levonorgestrel. These failure rates have been reported in previous studies. To have a power of 80% in a 5%-level two-sided test and assuming 10% loss to follow-up, a sample size of 1340 women per group (4020 total) was required. To be conservative, we increased our target sample size to 4200. This sample size would have 78% power to show non-inferiority (one-sided equivalence) between failure rates in the two levonorgestrel regimens within a margin of equivalence of 1·1% on the absolute scale with a 95% CI if the true failure rates are 1·1% in both regimens (as observed previously[1]). However, the power would be only 47% if the true failure rates are 2·9% in both regimens.

We excluded women who were lost to follow-up from the efficacy analysis, because we did not know their outcome. We also decided a priori to exclude women who requested emergency contraception if their single act of unprotected intercourse occurred after missed menses, but who had erroneously been treated. Otherwise, the analysis was as per randomisation. For the safety analysis, all women with at least some safety information were included.

To compare the efficacy of the three treatments, we calculated relative risks by standard methods, and their 95% CIs with Taylor series. We calculated the ratio of observed to expected pregnancies, the prevented fraction and its 95% CI in each group assuming the binomial distribution and taking into account the imprecision of conception probability estimates.[5] To take into account the standardisation by the expected pregnancies, we calculated the ratio of the standardised rates and its 95% CI assuming a ratio between two Poisson variables. We used logistic regression with SAS software (version 8) to adjust for centres and to test for interactions between regimens and the other four variables—centre, delay in treatment, additional acts of intercourse, and ethnic origin.

To investigate the observed pregnancies in greater detail we undertook subgroup analyses to compare the efficacy between regimens in women who adhered to protocol and were treatment compliant. We stratified our analyses by delay in treatment administration (women treated within 72 h and from 73 to 120 h after unprotected intercourse), acts of protected intercourse after treatment (yes/no), unprotected acts of intercourse (yes/no), and ethnic group (Chinese and non-Chinese).

We investigated the effect of delay in treatment on treatment efficacy in two ways. First, we compared the efficacy of each regimen among women treated within 72 h with those treated from 73 to 120 h after unprotected sex using a relative risk and a χ^2 test. Second, we calculated a χ^2 for trends with the crude pregnancy rates for each 24-h interval of delay.

Before the trial started we agreed that a failure rate of any of the three treatments higher than the 3·2% rate associated with the Yuzpe regimen[1] was not acceptable. We decided that if the lower 95% CI on the failure rate in a group was greater than 3·2%, we would investigate the reasons for such high failure rates, but there was no stopping rule.

Role of the funding source

UNDP/UNFPA/WHO/World Bank Special Programme of Research, Development, and Research Training in Human Reproduction funded this study. The donors and sponsors of the programme had no role in the study design, data collection, data analysis, data interpretation, writing of the report, or the decision to submit the paper for publication.

Results

4136 women were enrolled in the trial by 15 centres; each centre recruited between 122 and 447 women (table 1), 1380 were assigned mifepristone, 1379 single-dose levonorgestrel, and 1377 two-dose levonorgestrel (figure 1). We did not record the number of women who requested emergency contraception but were not enrolled.

	Mifepristone			Single-dose levonorgestrel			Two-dose levonorgestrel			All regimens		
	Enrolled	Lost to follow-up	Pregnant	Enrolled	Lost to follow-up	Pregnant	Enrolled	Lost to follow-up	Pregnant	Enrolled	Lost to follow-up	Pregnant
Beijing	99	0	1	100	0	3	97	0	3	296	0	7
Geneva	92	4	2	93	7	2	96	3	1	281	14	5
Helsinki	40	0	1	41	1	1	41	1	0	122	2	2
Hong Kong	99	8	1	99	4	1	99	7	1	297	19	3
Ljubljana	50	0	0	49	0	1	48	0	2	147	0	3
Manchester	49	2	1	49	3	0	49	2	0	147	7	1
Nanjing	149	0	2	149	2	3	149	0	3	447	2	8
New Delhi	48	5	0	49	0	3	50	0	2	147	5	5
Shanghai (IFPTI)	149	0	4	149	3	1	149	1	5	447	4	10
Shanghai (SIPPR)	149	0	4	149	0	2	149	1	4	447	1	10
Stockholm	99	1	1	100	1	1	98	4	1	297	6	3
Szeged	108	0	2	107	0	0	106	0	0	321	0	2
Tbilisi	49	0	0	49	0	0	49	0	0	147	0	0
Tianjin	100	0	1	97	0	1	99	0	0	296	0	2
Ulaanbaatar	100	0	1	99	1	1	98	0	2	297	1	4
All centres	1380	20	21	1379	22	20	1377	19	24	4136	61	65

IFPTI=Institute of Family Planning Technical Instruction. SIPPR=Shanghai Institute of Planned Parenthood Research.

Table 1: **Pregnancies by centre and treatment group**

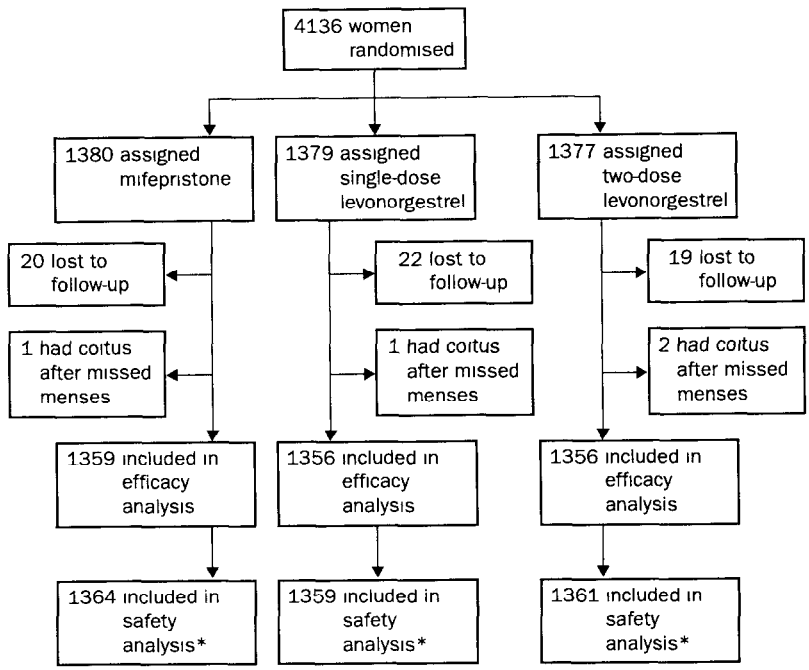

Figure 1: **Trial profile**
*Side-effects information available if first follow-up visit took place.

All women received the first dose of treatment. We did not have information about the second dose intake for 62 women, most of whom (52) missed the first follow-up visit (information on the second dose was collected retrospectively at this visit). 36 women took the second dose 24 h or more after the first dose, and 21 vomited in the first hour after either tablet intake. In all, 117 women had partial non-compliance or their compliance could not be assessed (two women had more than one reason for non-compliance).

Of 4136 women enrolled, 61 were lost to follow-up (1·5%), and we did not know the outcome of their treatment. Four women (0·1%) who requested emergency contraception and declared having unprotected intercourse after the expected date of menses were excluded from the efficacy analysis. Thus, 4071 women with outcome information remained in this analysis (figure 1), of whom 2202 (54%) were Chinese and 1869 (46%) non-Chinese, and most of these were white.

Baseline characteristics were similar among the three treatment groups (table 2). Women were young (mean age 27 years; range 14–52 years), had a mean weight of 56 kg, and about a quarter (26% [1075/4071]) had used emergency contraception in the past. More than half (60% [2460]) had been pregnant before, but there was a large variation between centres: from 8% (9/119) in Helsinki to 92% (410/445) in one of the Shanghai centres. The same trend was noted in the 48% (1971) of women who had had at least one induced abortion, which varied from 5% (6/119) to 78% (349/445) in the same centres. About half the women (52% [2131]) requested emergency contraception because they had not used any contraception at coitus, 44% (1799) reported condom failure, and 3–4% (141) had another contraceptive fail. In all, 44% (1792) of women requested treatment within 24 h, 72% (2933) within 48 h, and 88% (3596) within 72 h.

The 61 women lost to follow-up were younger (mean 22 years) than the other women, a smaller percentage had been pregnant before (33% [20]) and had induced abortion (28% [17]). The proportion of Chinese women was smaller among those lost to follow-up (43% [26]).

Of the 4071 women included in the efficacy analysis, 65 were pregnant (table 3). There were no significant differences in pregnancy rates between the three regimens (p=0·83). Adjustment for centre with the Mantel-Haenszel procedure produced almost identical results. There was no statistical heterogeneity between centres (p=0·84 for the comparison of the two levonorgestrel groups, p=0·49 for that of the two levonorgestrel groups combined *vs* mifepristone, from Breslow-Day tests of homogeneity of odds ratios). The four women excluded from the analysis who requested emergency contraception after the expected date of menses, were not pregnant. One pregnancy in the two-dose levonorgestrel group was in the fallopian tube, all others were intrauterine. All pregnant women opted to have induced abortion.

Unreported pregnancies in women lost to follow-up, if imbalanced, could bias the results; however, we have no reason to believe that this situation is likely to have happened.

The number of expected pregnancies if no treatment had been given, and the proportion prevented by treatment are shown in table 3. The risk of pregnancy for the single-dose levonorgestrel group compared with the

	Mifepristone (n=1359)	Single-dose levonorgestrel (n=1356)	Two-dose levonorgestrel (n=1356)
Demographic and anthropometric variables, mean (SD)			
Age (years)	27·2 (7·0)	27·1 (7·2)	27·4 (7·1)
Weight (kg)*	56·5 (8·6)	56·0 (8·7)	56·4 (8·7)
Height (cm)†	163·4 (5·8)	163·1 (6·2)	163·0 (6·0)
Length of cycle (days)‡	29·3 (2·7)	29·2 (2·7)	29·3 (2·8)
Duration of menstrual flow (days)	5·0 (1·3)	5·0 (1·3)	5·0 (1·2)
Time between ovulation and intercourse	0·6 (5·3)	0·8 (5·2)	0·6 (5·3)
Ethnic group			
Chinese	737 (54%)	733 (54%)	732 (54%)
Other Asian/black	157 (12%)	163 (12%)	166 (12%)
White	465 (34%)	460 (34%)	458 (34%)
History			
Pregnancy	832 (61%)	804 (59%)	824 (61%)
Induced abortion	681 (50%)	632 (47%)	658 (49%)
Use of EC	340 (25%)	390 (29%)	345 (25%)
Other contraceptive methods	1255 (92%)	1235 (91%)	1248 (92%)
Reasons for requesting EC			
No method	720 (53%)	725 (54%)	686 (51%)
Condom failure	585 (43%)	590 (44%)	624 (46%)
Other contraceptive failure	54 (4%)	41 (3%)	46 (3%)
Time from coitus to treatment (h)§			
0–24	598 (44%)	622 (46%)	572 (42%)
25–48	403 (30%)	377 (28%)	361 (27%)
49–72	214 (16%)	199 (15%)	250 (18%)
73–96	99 (7%)	87 (6%)	101 (7%)
>96	38 (3%)	63 (5%)	63 (5%)

EC=emergency contraception. *Two missing observations †Three missing observations ‡Five missing observations. §24 missing observations.

Table 2: **Baseline characteristics**

	Rate			Prevented fraction (95% CI)	Relative risks* (95% CI)	Relative risks* (95% CI)
	n	Pregnancies	Expected pregnancies			
Mifepristone	1359	21 (1·55%)	108	81% (69·2–87·8)	1	0·87 (0·49–1·56)
Single-dose levonorgestrel	1356	20 (1·47%)	111	82% (70·9–88·7)	0·95 (0·52 to 1·75)	0·83 (0·46–1·50)
Two-dose levonorgestrel	1356	24 (1·77%)	106	77% (64·9–85·4)	1·15 (0·64 to 2·05)	1
All levonorgestrel	2712	44 (1·62%)	216	80% (71·2–85·6)	1·05 (0·63 to 1·76)	-

*Crude relative risks.

Table 3: **Pregnancy rates and prevented fractions**

two-dose group, adjusted for the expected pregnancies in each group, was 0·80 (0·42–1·51). That for levonorgestrel (the two regimens combined) compared with mifepristone was 1·05 (0·61–1·85). These results are very similar to those noted before adjustment (table 3).

We repeated the analysis excluding 174 women who were not eligible according to inclusion and exclusion criteria and should not have been enrolled, or who did not comply fully with the treatment. Among these, 127 were not eligible: 32 were treated after 120 h had elapsed from the single act of unprotected intercourse, 16 had cycle length shorter than 24 days or longer than 42 days, one had used hormonal methods of contraception during the current cycle and 84 had used rhythm methods (six women met more than one exclusion criterion). The remaining 47 excluded women were partly non-compliant, or those with compliance information missing who were still left after the previous exclusions. Thus, of the 3897 women left after exclusions, 1·4% (18/1312) were pregnant in the mifepristone group, 1·5% (20/1303) in the single-dose levonorgestrel group and 1·7%(22/1282) in the two-dose levonorgestrel group. Comparisons of pregnancy proportions did not differ greatly from those noted before exclusions: the crude relative risk of pregnancy for single-dose levonorgestrel compared with two-dose levonorgestrel was 0·89 (0·49–1·63); that for levonorgestrel (the two regimens combined) compared with mifepristone was 1·18 (0·68–2·05).

We investigated whether the length of time between unprotected intercourse and treatment (ie, delay of treatment) was an effect modifier, and whether it also had an effect on efficacy (table 4). There was no evidence of an interaction between regimens and timing of treatment within 72 h of unprotected intercourse, or after 72 h (p=0·90). For the three regimens combined, women who were treated after 72 h had higher pregnancy rates, 2·4% (11/451) than those treated within 72 h, 1·5% (54/3596), but the difference was not significant (p=0·16). However, there was a significant trend in pregnancy rates in the 5 successive days from the time of unprotected intercourse (χ^2 5·5, p=0·0190; p=0·0034 from logistic regression). The numbers were too few to assess this trend separately for mifepristone and for the two levonorgestrel groups: the pregnancy rates on days 1, 2, 3, 4, and 5 were 1·2% (7/598), 1·2% (5/403), 2·8% (6/214), 1·0% (1/99), and 5·3% (2/38), respectively, in the mifepristone group. The corresponding results for both levonorgestrel groups combined were 1·7% (20/1194), 0·7% (5/738), 2·5% (11/449), 1·1% (2/188), and 4·8% (6/126), respectively.

Having intercourse (with or without contraception) between treatment and expected menstruation resulted in higher pregnancy rates (p=0·0005): 2836 women reported not having had intercourse, and 1235 women reported at least one act of intercourse. Of women who did not have coitus after treatment, there were 32 pregnancies (1·1%) and of women who did have intercourse, there were 33 pregnancies (2·7%). There was no interaction by regimen (p=0·18; table 4). On the other hand, having unprotected intercourse (without contraception) between treatment and expected menstruation resulted in much higher pregnancy rates in the mifepristone group (9/41 [22·0%]) than the levonorgestrel groups (4/61 [6·6%]). By contrast, in women who did not report having intercourse after treatment, there were 12 pregnancies out of 1318 (0·9%) in the mifepristone group and 40 out of 2651 (1·5%) in the two levonorgestrel groups combined; the interaction was significant (p=0·02).

Chinese women were pregnant more frequently than non-Chinese, but the difference was not significant (p=0·45; table 4). Of 2202 women in Chinese centres who completed the follow-up, 40 (1·8%) were pregnant.

	Group	Observed pregnancies/total	Prevented fraction (95% CI)
Delay in treatment after intercourse (days)*			
1–3	Mifepristone	18/1215 (1·48%)	82% (70·5 to 89·0)
	Single-dose levonorgestrel	16/1198 (1·34%)	84% (73·0 to 90·5)
	Two-dose levonorgestrel	20/1183 (1·69%)	79% (66·2 to 86·8)
4–5	Mifepristone	3/137 (2·19%)	58% (–23·8 to 86·0)
	Single-dose levonorgestrel	4/150 (2·67%)	63% (1·5 to 85·7)
	Two-dose levonorgestrel	4/164 (2·44%)	60% (–5·9 to 84·6)
Intercourse after treatment†			
Yes	Mifepristone	14/443 (3·16%)	60% (30·5 to 76·6)
	Single-dose levonorgestrel	7/404 (1·73%)	81% (59·0 to 90·9)
	Two-dose levonorgestrel	12/388 (3·09%)	64% (36·0 to 80·0)
No	Mifepristone	7/916 (0·76%)	91% (79·7 to 95·5)
	Single-dose levonorgestrel	13/952 (1·37%)	83% (69·0 to 90·1)
	Two-dose levonorgestrel	12/968 (1·24%)	83% (70·0 to 90·8)
Ethnic group‡			
Chinese	Mifepristone	13/737 (1·76%)	78% (60·6 to 87·3)
	Single-dose levonorgestrel	11/733 (1·50%)	81% (65·0 to 89·6)
	Two-dose levonorgestrel	16/732 (2·19%)	70% (50·3 to 82·3)
Non-Chinese	Mifepristone	8/622 (1·29%)	84% (67·5 to 92·2)
	Single-dose levonorgestrel	9/623 (1·44%)	83% (66·7 to 91·3)
	Two-dose levonorgestrel	8/624 (1·28%)	85% (68·7 to 92·4)

*p delay=0·17 p regimen×delay=0·90 †p further acts p=0·0005 p regimen×further acts=0·18 ‡p ethnic group=0·45. p regimen×ethnic group=0·79

Table 4: **Efficacy analysis stratified by intercourse-treatment interval, intercourse after treatment, and ethnic group**

	Group	Number of cases	p*
Nausea	Mifepristone	196/1364 (14%)	0 86
	Single-dose levonorgestrel	189/1359 (14%)	
	Two-dose levonorgestrel	199/1361 (15%)	
Vomiting	Mifepristone	12/1364 (1%)	
	Single-dose levonorgestrel	19/1359 (1%)	0 37
	Two-dose levonorgestrel	19/1361 (1%)	
Diarrhoea	Mifepristone	61/1364 (5%)	
	Single-dose levonorgestrel	53/1359 (4%)	0 24
	Two-dose levonorgestrel	44/1361 (3%)	
Fatigue	Mifepristone	208/1364 (15%)	
	Single-dose levonorgestrel	184/1359 (14%)	0 30
	Two-dose levonorgestrel	182/1361 (13%)	
Dizziness	Mifepristone	123/1364 (9%)	
	Single-dose levonorgestrel	132/1359 (10%)	0·82
	Two-dose levonorgestrel	126/1361 (9%)	
Headache	Mifepristone	140/1364 (10%)	
	Single-dose levonorgestrel	142/1359 (10%)	0 71
	Two-dose levonorgestrel	130/1361 (10%)	
Breast tenderness	Mifepristone	114/1364 (8%)	
	Single-dose levonorgestrel	113/1359 (8%)	0 99
	Two-dose levonorgestrel	115/1361 (8%)	
Lower abdominal pain	Mifepristone	191/1364 (14%)	
	Single-dose levonorgestrel	183/1359 (14%)	0 72
	Two-dose levonorgestrel	198/1361 (15%)	
Bleeding	Mifepristone	258/1364 (19%)	
	Single-dose levonorgestrel	426/1359 (31%)	<0·0001
	Two-dose levonorgestrel	426/1361 (31%)	
Delay of menses more than 7 days†	Mifepristone	118/1327 (9%)	
	Single-dose levonorgestrel	62/1334 (5%)	<0 0001
	Two-dose levonorgestrel	63/1332 (5%)	

*Bonferroni adjustment for simultaneous inferences. significance at 1% level if p<0 0010. †Non pregnant only

Table 5: **Side-effects within 7 days and delay of menses**

Of the 1869 corresponding women in non-Chinese centres, 25 (1·3%) were pregnant. The comparison of regimens stratified by ethnic group yielded similar results to those without stratification (p=0·79 for the regimen by ethnic group interaction).

In the mifepristone group, there was no association between the timing of treatment in relation to the cycle day and the timing of menses (p=0·79 for the linearity component from a linear model adjusting for centres). For the two levonorgestrel groups combined, the earlier in the cycle the treatment occurred, the earlier the menses started (the linearity component was significant, p<0·0001).

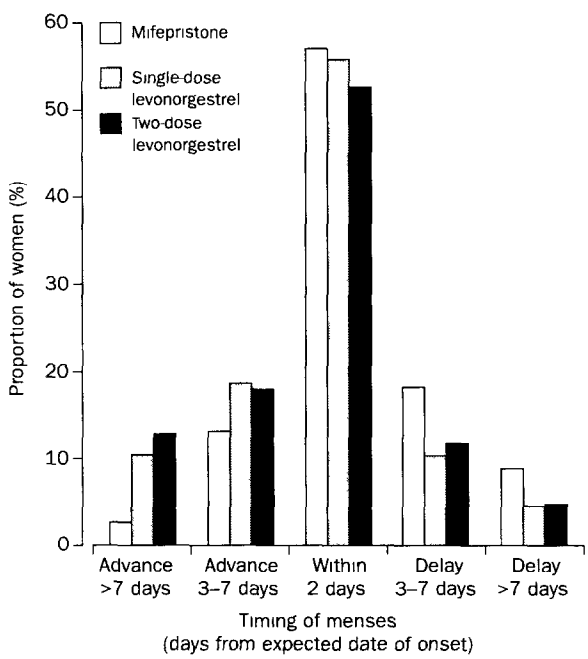

Figure 2: **Timing of menses after postcoital contraception**

Women recorded side-effects day by day, and complaints were uncommon in all treatment groups in the 7 days after the start of treatment (table 5). Only about 1% (50/4084) of women reported vomiting. There was no significant difference in the proportion of women with each side-effect between regimens except for bleeding and delay of menses for more than 7 days. During the first day after treatment, 9% of women or less reported side-effects (data not shown). During the second and third day combined, these proportions were all less than 11% and less than 8% during days 4 to 7.

Bleeding within the first 7 days was more common in the two levonorgestrel groups (31% or 852/2720) than the mifepristone group (19% [258/1364], p<0·0001, table 5). If women who had menses starting within these 7 days are excluded, the rates were about 16% for the two levonorgestrel groups (168/1011 and 150/967 for single-dose and two-dose levonorgestrel, respectively) and 9·4% (107/1142) for mifepristone (p<0·0001), so that bleeding not related to menses seemed to be more common in women who had received levonorgestrel.

More than half the women in all groups had menses within 2 days of the expected date (figure 2). More of the remaining women in the two levonorgestrel groups tended to have menses earlier than expected, and more women in the mifepristone group tended to have it later (p<0·0001). About 9% (118/1327) of women in the mifepristone group had a delay of more than 7 days in the onset of the first menses after treatment, compared with 5% (125/2666) in the two levonorgestrel groups combined.

Although the total rate of side-effects was low, there were differences between centres, such that women in developed countries reported more side-effects after treatment than women in developing countries. For example, within 7 days of treatment, three women out of 147 (2%) reported nausea in New Delhi, but 41 out of 147 (28%) did so in Manchester. There were three reports of serious adverse events during the trial: one ectopic pregnancy that required surgical treatment (two-dose levonorgestrel group); one of pyelonephritis that required treatment in hospital between treatment and follow-up (mifepristone group); and one of a ruptured corpus luteum cyst that required surgery between treatment and follow-up (single-dose levonorgestrel group). There is no evidence of any relation between these events and trial treatment.

Discussion

We started this trial with the objective of comparing the efficacy of three regimens in prevention of pregnancy, and we noted no difference between the treatments. However, because of our sample size, we cannot discard the possibility that the single-dose levonorgestrel regimen increases the risk of pregnancy up to 1·5-fold compared with the two-dose regimen, or that the two-dose regimen increases the risk of pregnancy up to more than two times that of the single dose regimen. To prove equivalence within a smaller margin would have required a larger trial.

In our two earlier international trials, we reported slightly lower pregnancy rates than in this trial for the two-dose levonorgestrel regimen,[1] and for the single-dose regimen of 10 mg of mifepristone.[4] These differences can be explained by chance, because they were not significant (p=0·27 and p=0·76, respectively, from a continuity-adjusted χ^2 test).

After adjustment for expected pregnancies with the same conception probabilities,[1] the two-dose levonorgestrel regimen in the previous trial prevented 89% of pregnancies,[1] but in this trial it prevented 79% when administered within 72 h after coitus. As for mifepristone, in the previous trial the 10 mg dose prevented 85% of pregnancies[4] compared with 81% in this trial.

However, the comparison of pregnancy rates and prevented fractions between trials is subject to bias, because the actual rates will depend on the sample of women studied. Inclusion and exclusion criteria might vary between protocols, and women's characteristics could influence results: cultural and social determinants of women's reporting might also vary across trials. When seeking post-coital emergency contraception, some women could be reluctant to provide reliable information—for example, they might have had several earlier acts of intercourse in that cycle, or even suspect an early pregnancy, which cannot be detected at admission. Thus, our comparison of efficacy between groups in this trial is unbiased, but we warn against the limitations of absolute estimates of pregnancy rates and prevented fractions within studies, and hence also of crude comparisons between studies.

We are aware of only one published study[6] comparing levonorgestrel (two 0·75 mg doses) and 10 mg mifepristone, which was done by S Wu and colleagues using locally manufactured drugs, and launched at about the same time as this trial. It was a double-blind, randomised, multicentre trial with 643 and 633 women, respectively, in the levonorgestrel and mifepristone groups. The treatment was administered up to 72 h after coitus. The failure rate of the two-dose regimen of levonorgestrel was 3·1% and that of mifepristone 1·4% (relative risk 2·17, 95% CI 1·00–4·77). In our trial the failure rates of the two regimens among Chinese women within 72 h of coitus were 2·2% and 1·8%, respectively (1·24, 0·60–2·56), and were not significantly different. In addition to the differences between the participants in the two trials, there might be also a difference in the characteristics of the drugs used.

For all treatment regimens combined, pregnancy rates were slightly higher, in Chinese than non-Chinese women, although not significantly so (1·8% *vs* 1·3%, respectively). We observed the same trend in our previous trial with levonorgestrel (2·0% *vs* 0·8%) as well as with the Yuzpe regimen (5·7% *vs* 2·3%), but these differences were not significant.[1] We are not aware of higher pregnancy rates in Chinese who use regular hormonal contraception than women of other ethnic origins. However, Chinese women had higher pregnancy rates in studies of the efficacy of intrauterine devices[7] and of women with lactational amenorrhoea.[8] In addition to ethnic differences in metabolism of steroids,[9] there could also be variations in fertility between populations.

We have reported previously, a significant increasing trend in failure rates with delay in treatment for levonorgestrel and the Yuzpe regimen combined.[10] However, when considering levonorgestrel alone, the numbers were small and the trend was not significant. There was no evidence that a delay in the administration of mifepristone affected efficacy.[4] When we compared the efficacy of treatment in women starting the treatment within 3 days of unprotected intercourse and those starting treatment with a delay of 4 or 5 days, we did not detect an effect of treatment delay on the efficacy. However, a trend towards a lower efficacy with longer delay was present for the three regimens combined when considering the pregnancy rates in the 5 successive days. An assessment of this trend is desirable for the two drugs separately, but the small number of women given delayed treatments in this trial makes our estimation very imprecise. There is a need for meta-analyses of the two regimens, with pooled data from different trials at the patient level and adjustment for confounders to obtain more power in the assessment of this clinically relevant effect. The adjustment for confounders is important because the comparison between delay categories is observational in nature—ie, it is not randomised.

Side-effects were rare, but there was variation between centres such that women in developed-country centres reported side-effects more often than women in developing countries. Overall, women reported fewer side-effects in this trial after levonorgestrel than did those in our previous trial.[1] For example, the occurrence of nausea after two doses of levonorgestrel was 23% in the previous trial and about 15% in this trial, and the rates of vomiting were 5·0% and 1·4%, respectively. Because proportions of women with side-effects vary widely between centres, the variation between trials could be explained by different centres participating in the trials.

Mifepristone has been shown to delay ovulation,[11] which means a longer cycle and later return of menses than if ovulation was not delayed. Furthermore, there is a continued risk of pregnancy after treatment if women have further unprotected intercourse. Our results confirm this finding, because we noted that the delay of menses happened significantly more often in the mifepristone group, and pregnancy rate was as high as 22% in women who continued to have unprotected coitus after mifepristone treatment compared with 0·9% in women who did not have unprotected intercourse after treatment in that group. For example, ultrasonography showed that one woman in the mifepristone group had conceived more than 3 weeks after treatment. When counselling women on emergency contraception, the risk of pregnancy after treatment should be highlighted, especially if mifepristone is used. Contraception should be recommended in cases where abstinence is not possible.

The occurrence of delay in the start of the next menses was related to the dose of mifepristone in the previous mifepristone trial.[4] The proportion of women in the 10 mg group who had a delay of more than 7 days was 18% (97/553) in that trial, and 9% (117/1326) in this one ($p<0·0001$ from a χ^2 test). The difference might be partly attributable to the fact that in the previous trial, any bleeding that occurred within 5 days of treatment was regarded as treatment-related and not as menses, and thus, menses delay might have been somewhat over-reported.

We believe that this trial has internal validity because treatments were randomly allocated, participants, clinicians, and investigators were unaware of treatement allocation, and our sample size was large enough to show a clinically relevant difference if it existed. This trial also has external validity, because it enrolled women of several different populations in developing and developed countries.

Our findings show that the levonorgestrel dose does not need to be split, but that a single dose of 1·5 mg can be used. The use of a single dose simplifies the use of levonorgestrel for emergency contraception without an increase in side-effects. Compared with mifepristone, either of the levonorgestrel regimens has the advantage of being associated with early, rather than late, menses after treatment. With early or on-time menses, women are relieved from anxiety about an unwanted pregnancy sooner, and can begin a regular and effective method of contraception more quickly than if menstruation is delayed. Evidence of higher efficacy with earlier treatment

from this trial was weak, suggesting that further research is needed. In any case, even if a declining trend in efficacy with time were verified, the regimens studied still prevent a high proportion of pregnancies even up to 5 days after coitus.

Contributors

H von Hertzen, in collaboration with the members of the steering committee, was responsible for the conception of the trial and selection of centres. H von Hertzen and G Piaggio prepared the protocol. H von Hertzen supervised the trial. J Ding, J Chen, S Song, G Bártfai, E Ng, K Gemzell-Danielsson, A Oyunbileg, S Wu, W Cheng, F Ludicke, A Pretnar-Darovec, R Kirkman, S Mittal, A Khomassuridze, and D Apter contributed to the final trial protocol and implemented the trial in their respective countries. G Piaggio and A Peregoudov were responsible for data management and the statistical analysis. H von Hertzen and G Piaggio wrote the paper with inputs from the investigators.

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Conflict of interest statement

None declared

Acknowledgments

The study was funded by the UNDP/UNFPA/WHO/World Bank Special Programme of Research, Development, and Research Training in Human Reproduction. Gedeon Richter, Budapest, Hungary provided levonorgestrel and placebo tablets, and Roussel-Uclaf, Romainville, France, provided the mifepristone and placebo used in the study.

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APPENDIX 6

Notification from European Medical Authorities dated April 30, 2003
(Change of labeling to single intake of 1.5 mg levonorgestrel for emergency contraception)

AGENCE FRANÇAISE DE SECURITE SANITAIRE DES PRODUITS DE SANTE

Direction de l'Evaluation
des Médicaments et des Produits Biologiques

Mutual Recognition Procedures
Coordination Unit
Tél. : (33) 1 55 87 32 98
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Saint-Denis, April 30th, 2003

To: Mrs Christa Wirthumer Hoche (Austria)
Mrs Natacha Grenier (Belgium)
Mrs Birgit Jensen (Denmark)
Mrs Anne-Mari Hintikka (Finland)
Dr Peter Bachmann (Germany)
Mrs J.Yotaki / V. Revithi (Greece)
Mr Pasqualino Rossi (Italy)
Mrs Jacqueline Genoux-Hames (Luxemburg)
Mrs Truus Janse-de Hoog (Netherlands)
Mrs Gunilla Edman-Bergstrand (Sweden)

Cc Company: Mme Vincent
HRA Pharma
fax : 01 40 33 12 31

From: Ms Christelle Bouygues /Mrs Françoise Portefaix
Clinical assessors: Mrs L. Kapetanovic/Mrs L. Duranteau

Re.: **NORLEVO - Type II variation**
FR/H/146/01/W05 : To update the SPC (sections 4.2 with consequential changes on section 4.8)
FVAR

Dear colleagues,

Further to circulation of the final assessment report and response to the last Danish comments, we have received a positive opinion from Danemark, Finland, Sweden and Belgium, and no comments from the other concerned member states.

Consequently, according to the regulation EC/541/95 as amended - Article 7, this variation is considered as positively ended on April 30th, 2003 and will have to be implemented by May 30th, 2003 at the latest.
You will find hereafter the final agreed SmPC to be implemented.

Best regards,

Christelle Bouygues
MRP Coordinator

Summary of Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT

Norlevo, 750 microgram tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 750 micrograms levonorgestrel
For excipients, see 6.1.

3. PHARMACEUTICAL FORM

Tablet
White, round tablet with no marking

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Emergency contraception within 72 hours after an unprotected sexual intercourse or in case of failure of a contraceptive method, such as:

- ruptured or forgotten condom;
- forgotten oral contraceptive pill beyond the maximum acceptable time lag since the last intake;
- expelled intrauterine device;
- early removal or dislodgment of a vaginal diaphragm or of a contraceptive cap;
- failure of the coitus interruptus method;
- sexual intercourse during the supposedly fertile period when relying on periodic abstinence (temperature method);
- rape.

4.2 Posology and method of administration

The treatment necessitates the intake of **two tablets in a single administration**. The efficacy of the method is higher the sooner after the unprotected intercourse the treatment is initiated. **Therefore, the two tablets must be taken as soon as possible, preferably within 12 hours, after the unprotected intercourse** and no longer than 72 hours (3 days) after the intercourse.

Norlevo can be taken at any moment during the menstrual cycle.

After using an emergency contraception, it is recommended to use a local contraceptive mean (condom, spermicide, cervical cap) until the next menstrual periods resume. The use of Norlevo does not contraindicate the continuation of regular hormonal contraception.