Single dose mifepristone, single dose levonorgestrel and 2-dose levonorgestrel are all equally safe and effective as emergency contraception

Abstracted from: von Hertzen H, Piaggio G, Ding J et al. Low dose mifepristone and two regimens of levonorgestrel for emergency contraception: a WHO multicentre randomised trial. *Lancet* 2002; 360: 1803–1810.

BACKGROUND Emergency contraception is increasingly used in both developed and developing countries. In some countries, emergency contraceptives are available over the counter without prescription. It is important that clinicians, policymakers and health managers are aware of the most effective emergency contraceptive options. There is evidence that a single dose of mifepristone or two doses of levonorgestrel 12 hours apart are effective for preventing pregnancy. The comparative efficacy of these strategies remains unclear.

OBJECTIVE To compare the efficacy of a single 10 mg dose of mifepristone; two 0.75 mg doses of levonorgestrel 12 hours apart or a single dose of 1.5 mg levonorgestrel for emergency contraception.

SETTING Fifteen family planning clinics in China, Finland, Georgia, Hungary, India, Mongolia, Slovenia, Sweden, Switzerland and the United Kingdom; timeframe not specified.

METHOD Randomised double-blind trial.

PARTICIPANTS Four thousand and seventy-one women with regular menstrual cycles who requested emergency contraception within 120 hours of intercourse. Mean age 27 years (range 14 to 52); 54% Chinese, 34% white.

INTERVENTION Women received a single dose of 10 mg mifepristone, 1.5 mg levonorgestrel or two doses of 0.75 mg levonorgestrel 12 hours apart.

OUTCOMES Unintended pregnancy; adverse effects; timing of next menstruation.

MAIN RESULTS There was no difference in unintended pregnancy between groups (1.5% mifepristone, 1.5% single dose levonorgestrel, 1.8% 2-dose levonorgestrel). Adverse effects were mild and did not differ significantly between groups. Most women menstruated within 2 days of the expected date. Women who received levonorgestrel tended to menstruate earlier than those who received mifepristone.

AUTHORS' CONCLUSIONS If taken within 5 days of unprotected intercourse, single dose mifepristone, single dose levonorgestrel and 2-dose levonorgestrel are equally safe and effective for preventing pregnancy in healthy women. A single dose of 1.5 mg levonorgestrel can be substituted for two 0.75 mg doses 12 hours apart.

NOTE The authors state that analysis was by intention to treat, but some participants were excluded from the final analysis. The sample did not reach the estimated required size so the study may not be adequately powered to detect differences between groups.

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Commentary I

Relevance

This large, well-conducted multicentre study reports that levonorgestrel for emergency contraception can be given in one dose instead of two and that the treatment period can be extended from 3 to 5 days after unprotected intercourse. For treatment within 3 days, the estimated proportions of prevented pregnancy were 84% for 1-dose levonorgestrel (95% CI 73 to 91), 79% for 2-dose levonorgestrel (95% CI 66 to 87) and 82% for mifepristone (95% CI 70 to 89).

The contraceptive efficacy of 2-dose levonorgestrel and Yuzpe regimens begun within 3 days (72 hours) of unprotected intercourse depends on how quickly treatment is administered. The sooner after intercourse treatment is administered, the more efficacious it is.[1]

In this study, treatment within 3 days of unprotected intercourse was associated with lower pregnancy rates (1.5%) compared with treatment 4 or 5 days after intercourse (2.4%). The estimated prevented proportion of pregnancies was about 20 percentage units higher when treatment started within 3 days compared with treatment started beyond 3 days. For instance, the prevented fraction of pregnancies was 84% for single dose levonorgestrel administered within 3 days compared with 63% for treatment started on the 4th or 5th day after intercourse. This difference was not statistically significant, even when data from the three regimens were pooled (relatively few women started treatment more than 3 days after intercourse). In the pooled data, the trend between time to the start of treatment and increasing pregnancy rate was statistically significant.

Previous large studies suggest that hormonal emergency contraception is safe. A study of the Yuzpe regimen and venous thromboembolism, the most frequent cardiovascular adverse effect of hormonal contraceptives, found no increased risk associated with that regimen.[2] In von Hertzen's study, mild adverse effects were similar for the three regimens, except that intermenstrual bleeding occurred more often in the levonorgestrel groups (a third of the women) compared with the mifepristone group. Menstrual bleeding was also more often delayed by seven or more days in the mifepristone group (a tenth of the women).

Implications

One message from this study is that levonorgestrel can be administered in one dose with equal contraceptive efficacy and similar frequency of adverse effects as the 2-dose regimen. A second message is that levonorgestrel emergency contraception appears to be more effective the earlier it is used after unprotected intercourse, although for 1-dose levonorgestrel more information on this relationship is needed. A third message is that levonorgestrel has contraceptive effect when it is started on the 4th or 5th day after unprotected intercourse, even if it is less efficacious than earlier treatment. Thus, women should not be denied access to emergency contraception when they present 4 to 5 days after unprotected intercourse.

In this study, one 10 mg dose of mifepristone was equally efficacious for emergency contraception as one 1.5 mg dose of levonorgestrel. Unlike levonorgestrel, mifepristone is also effective for medical termination of early pregnancy, albeit in higher dosages and in combination with prostaglandin. This association between mifepristone and abortion has made it a controversial drug in many countries. It is approved for emergency contraception only in China.

Hormonal emergency contraception with the Yuzpe or levonorgestrel regimens has also been controversial in some countries. Some have argued that these drugs' mechanism of action is abortifacient. In countries where the Catholic church has strong political influence, some conservative groups have used this argument to oppose hormonal emergency contraception,[3] limiting access to this contraceptive method. There is strong evidence to suggest, however, that hormonal emergency contraception interferes with pre-fertilisation processes and is not abortifacient.[4–8]

Emergency contraception should be easily accessible for all women who wish to use it. The levonorgestrel regimen is sold over the counter in many countries to avoid unnecessary delays in starting treatment. In countries where it is only available by prescription, drug regulating authorities should rapidly make it available over the counter.

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Commentary 2

Relevance

This WHO study makes an important contribution to knowledge about emergency contraception. It confirms previous reports that mifepristone and levonorgestrel are effective as emergency contraception and that adverse effects are mild. It also suggests that these regimens are effective up to 5 days (120 hours) after unprotected intercourse. Earlier studies have reported effectiveness at 5 days for mifepristone,[1] but not levonorgestrel. Previous reports suggested a decline in efficacy with levonorgestrel and the Yuzpe method if treatment was delayed beyond 3 days after intercourse,[2] although the analysis combined both regimens. When considering levonorgestrel alone, there was no significant difference in efficacy at 3 and 5 days, although numbers were small.

Implications

One implication is that single dose levonorgestrel can be substituted for 2-dose levonorgestrel. These findings are in accordance with a recently published pharmacokinetic study which found similar levonorgestrel serum levels after two doses of 0.75 mg and one dose of 1.5 mg.[3] By changing the regimen to a single dose, treatment will be more convenient, compliance may increase and the number of unintended pregnancies may decrease.

This study also confirms previously reported findings about the mechanism of action with these methods. The mode of action with mifepristone or levonorgestrel is primarily due to inhibition (or delay) of ovulation rather than inhibition of implantation. In a previous study, when levonorgestrel was administered prior to luteinising hormone surge, ovulation was inhibited in most participants. Mifepristone either inhibited or delayed ovulation. Postovulatory treatment with levonorgestrel did not affect endometrial development and only minor alterations were noticed with mifepristone, not sufficient for preventing implantation.[4] Thus, emergency contraception with levonorgestrel or mifepristone does not act as abortifacient.

Von Hertzen and colleagues found that mifepristone was sometimes associated with slightly delayed menses, while levonorgestrel was more often associated with early menses. This confirms the effect on ovulation. The pregnancy rate was high after treatment, especially in the mifepristone group, indicating a delay in ovulation. One participant conceived more than 3 weeks after treatment. This has implications for counselling women on emergency contraception. Contraception should be recommended after treatment if abstinence is not possible.

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