Second, up to now, 3680 patients have been enrolled in ten randomised trials that have used procalcitonin to reduce patient exposure to antibiotics. Mortality was 10·10% (185/1829) for patients treated according to procalcitonin concentrations versus 9·94% (184/1851) in controls, confirming the safety of such a strategy.[1,2]

Third, our trial's sample was calculated to have sufficient power to exclude a 10% between-group mortality difference. Although we acknowledge that this margin is debatable, it is in accordance with the Infectious Diseases Society of America recommendation for non-inferiority trials assessing antibiotic treatment for severe community-acquired pneumonia.[3] The margin is also in accordance with guidelines issued by the Center for Drug Evaluation and Research Products, which also suggests the use of a 10% non-inferiority margin for assessment of new antibacterials.[4] Moreover, our study was designed assuming 35% mortality for control patients, whereas we recorded a crude mortality of 26·2% by day 60. This reduced mortality in the control group slightly increases the power of our study and, therefore, the probability of concluding non-inferiority.

Gibot also indicates that if control patients were managed according to current recommendations, our trial would have yielded negative results. We do not share this view, since the durations of antibiotic therapy in control patients were well in accordance with most recent international guidelines. Moreover, several studies have shown that guidelines are usually not applied strictly, or are only poorly applied.[5] Therefore, we do think that other strategies, based on the guidance of antibiotic treatment duration customised for each patient by using simple biomarkers, should be investigated to reduce antibiotic exposure in critically ill patients. Of course, we fully agree with Gibot that the appropriateness of starting or continuing antibiotics should not be based only on biomarkers. However, they can help us to take the best decision, keeping in mind that reducing antibiotic exposure is of utmost importance in an era of multiresistance.

We declare that we have no conflicts of interest.

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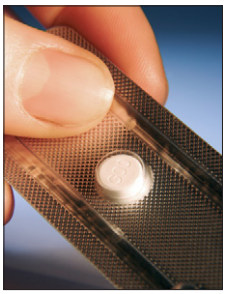
Ulipristal acetate for emergency contraception?

Anna Glasier and colleagues (Feb 13, p 555)[1] show the non-inferiority of ulipristal with respect to levonorgestrel as an emergency contraceptive in women presenting within 72 h of unprotected sexual intercourse.

The statement by Glasier and colleagues that the WHO trial comparing the Yuzpe regimen and levonorgestrel[2] "was not done to the current rigorous standards for clinical research" needs clarification: the WHO trial had only 2·2% missing primary endpoints and fulfilled the standards in place at the time it was undertaken. The exclusion of participants was based on admission criteria, applied before randomisation, and thus did not affect internal validity. If there was an overestimation of the efficacy, as argued by Glasier and colleagues, it was similar for the two regimens and did not compromise the aim of the trial—ie, to compare regimens rather than estimating their absolute efficacy.

The generalisability of the efficacy of ulipristal for women requesting emergency contraception within 120 h of unprotected sexual intercourse in Glasier and colleagues' trial is limited, since only 203 women (10·6%) presented between 73 and 120 h. A combined analysis[3] of two WHO studies[2,4] concluded that levonorgestrel remains effective up to and including the fourth day after unprotected intercourse, although it included only 314 women in the 73–120 h window from one of the trials.[4] A combined analysis of these two trials and two more WHO-sponsored studies (one published[5] and one in preparation) will soon be published to further evaluate the evidence for this conclusion.

If levonorgestrel is effective up to and including the fourth day, it would be ill-advised to replace its use, for women presenting before the fifth day, with a costly progestogen-receptor modulator. Such drugs, which may act in part through prevention of implantation, might not be accessible or acceptable to women in many countries.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GP worked with WHO from September, 1994, until December, 2008, and has participated as a statistician in the WHO trials cited in references 2 and 4. HvH was responsible for research on emergency contraception at WHO at the time when the cited studies were undertaken, but she is no longer working in the field of emergency contraception.

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Anna Glasier and colleagues[1] report on a randomised non-inferiority trial to compare the efficacy and safety of ulipristal acetate with levonorgestrel for emergency contraception. They conclude that ulipristal acetate provides women and health-care providers with an effective alternative for emergency contraception that can be used up to 5 days after unprotected sexual intercourse.

As Giuseppe Benagiano and Helena von Hertzen suggest in their associated Comment,[2] this conclusion is at least premature and in fact misleading. The design of Glasier and colleagues' trial (drafted and funded by the manufacturer of ulipristal) lacks the attributes to prove the efficacy of ulipristal in preventing pregnancy up to 5 days after unprotected intercourse.

First, the sample size is too small to permit comparisons between ulipristal and levonorgestrel administered 73–120 h after unprotected intercourse from reaching significance.

Second, a superiority trial is needed to provide evidence that ulipristal should be implemented in current care, since this product is less accessible (need for prescription), more costly (three times the price of levonorgestrel in Belgium), and does not yet have the same safety data as levonorgestrel. This industry-driven publication fails to support a change in current practice, where levonorgestrel is the first choice for emergency contraception if administered within 72 h of sexual intercourse and (if feasible) emergency insertion of a copper intrauterine device can be considered after 72 h. Further evidence is needed before a change in practice should be entertained.

We declare that we have no conflicts of interest.

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Authors' reply

Gilda Piaggio, Helena von Hertzen, Geert Herman Page, and Veerle Verhaeghe are unhappy with the methods or statistical analyses used in our published trial to compare levonorgestrel and ulipristal acetate for emergency contraception. The study was designed to provide a rigorous evaluation of efficacy in line with regulatory requirements for the approval of a new drug. As a registration trial, the protocol and statistical methods were reviewed by the US Food and Drug Administration before the start of the study, and the procedures, data collection, and analysis were subject to routine audit by independent quality assurance teams. Systematic pregnancy testing was done at enrolment and at follow-up, thereby ensuring accuracy and completeness of efficacy results.

Page and Verhaeghe criticise the trial for lacking the attributes to prove the efficacy of ulipristal acetate. Fundamental proof of efficacy of any method of emergency contraception would involve a randomised placebo-controlled trial. There has never been such a study, nor will there ever be one since no woman wanting to use emergency contraception to prevent unwanted pregnancy would be willing to use a placebo and no ethical committee would ever give approval to such a study. Like everyone else, we have relied on indirect measures of effectiveness of the drugs and we will never know how many pregnancies any emergency contraceptive *really* prevents.

As we discussed in the paper, there is good evidence that ulipristal acetate is much more effective than levonorgestrel at preventing ovulation at the time in the cycle when conception is most likely to occur.[1] Since we cannot get evidence of the true effectiveness of emergency contraception, biological plausibility of its effect is important. Yes, ulipristal acetate, as a new drug, is more expensive than levonorgestrel and purchasers will have to decide which emergency contraceptive product they provide on the basis of cost-effectiveness calculations. However, for individual women who want to prevent pregnancy after unprotected sexual intercourse, surely a method that is more likely to prevent ovulation would be the method of choice.

AG has received grants from HRA Pharma and Bayer Schering, and is a scientific advisory board member of HRA Pharma. EG is Chief Executive Officer of HRA Pharma.

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