Reminder: Most broad-spectrum antibiotics do not interact with combined oral contraceptives*

In 2011, United Kingdom guidelines were updated to remove the advice regarding the need for additional contraceptive precautions during courses of antibiotic treatment in women who are taking a combined oral contraceptive. This followed similar changes from the World Health Organisation in 2010. Bpac[nz] reported on this in June, 2011.

See: "New recommendations advise that the majority of broad-spectrum antibiotics do not affect the contraceptive effectiveness of the combined oral contraceptive", News in Brief, BPJ 36 (Jun, 2011).

> The majority of broad-spectrum antibiotics do not reduce the effectiveness of combined oral contraceptives and it is no longer necessary to advise women using a combined oral contraceptive and requiring a course of antibiotics to use additional contraceptive precautions.

This advice does not apply to every antibiotic and every situation:

- Women taking enzyme-inducing antibiotics, such as rifampicin and rifabutin, do require additional contraceptive precautions (see "Advice for women taking enzyme-inducing antibiotics")
- If an antibiotic causes vomiting or diarrhoea women should be advised to follow the "seven day rule", which refers to advice to use other methods of contraception (e.g. condoms or abstinence) during the period of illness and until seven active pills have been taken.

* This advice does not apply to enzyme inducing antibiotics such as rifampicin and rifabutin.

As the advice to use additional contraceptive methods with antibiotic treatment has been standard practice for many years, health professionals may find a reminder on the new advice helpful. In addition, many manufacturers have not updated their datasheets to reflect this information, which may be a source of confusion for both patients and health professionals.

Evidence for the change in advice

The ethinyloestradiol component of the combined hormonal contraceptive undergoes enterohepatic recirculation. This means it is metabolised in the liver and conjugated with glucuronide to form inactive conjugates, which are then excreted in the bile. Gastrointestinal bacteria cleave these conjugates and the oestrogen is reabsorbed.

The original theory was that if these bacteria are suppressed by the use of an antibiotic, the conjugates are not cleaved and therefore poorly absorbed, resulting in lower than normal concentrations of ethinyloestradiol and contraceptive failure.[1] However, evidence has accumulated suggesting that enterohepatic metabolism of ethinyloestradiol is not clinically important.[1]

Direct evidence

Several studies looking at combined oral contraceptives administered in conjunction with a range of non-enzyme inducing antibiotics have not shown any decrease in ethinyloestradiol levels.[2, 3] One study found that ciprofloxacin did not affect serum concentrations of gonadotrophins when used in combination with a combined oral contraceptive, and two other studies found no evidence of ovulation following

the combination of hormonal contraception and ciprofloxacin or ofloxacin (not available in New Zealand).[4, 5]

Indirect evidence

Other studies indirectly support the lack of a causal relationship between antibiotic use and contraceptive failure, e.g.:

- Serum contraceptive steroid levels and combined oral contraceptive efficacy do not appear to be affected in women with an ileostomy following lower bowel surgery, in whom enterohepatic circulation of ethinyloestradiol does not occur.[6]
- Most of the reports of contraceptive failure with antibiotic use comes from a time when ethinyloestradiol doses were higher (e.g. 50 micrograms). Currently ethinyloestradiol doses as low as 20 micrograms are considered to be an effective contraceptive so it seems unlikely that the small reduction in ethinyloestradiol levels following antibiotic use when using 30 to 50 microgram preparations would have resulted in contraceptive failure.[1]
- Reports of pregnancies have occurred in women taking erythromycin and fluconazole which actually increase levels of ethinyloestradiol.[1]

Alternative reasons for the anecdotal reports of contraceptive failure following antibiotic use could be:

- Contraceptive failure due to vomiting or diarrhoea induced by the antibiotic, or failure to take the contraceptive properly during a period of illness
- The total number of contraceptive failures is small when compared to the numbers of women worldwide using combined hormonal contraception. Given that there is an expected failure rate for oral contraceptives, the pregnancies that do occur when women are taking antibiotics are likely to be simply coincidental.[1]

While a cautious approach is often recommended in medicine, in this case, it is possible that these sorts of precautions may actually confuse patients, complicate pill taking and could have the opposite effect of increasing the failure rate of hormonal contraceptives.[7]

Advice for women taking enzyme-inducing antibiotics

The effectiveness of combined oral contraceptives (and other hormonal contraceptives) can be considerably reduced by the co-administration of medicines that induce hepatic enzymes, including the antibiotics rifampicin and rifabutin.

For short courses of rifampicin or rifabutin (two months or less), continue with a combined oral contraceptive containing ethinyloestradiol 30 micrograms or more daily and use a "tricycling" regimen, i.e. taking three packets of tablets without a break, followed by a shortened tablet-free interval of four days. Additional contraceptive precautions are required while taking rifampicin or rifabutin and for four weeks after stopping.

For a long-term course (over two months) of rifampicin or rifabutin, an alternative method of contraception (such as an IUD) is recommended and should also be continued for four weeks after stopping the enzyme-inducing medicine.

For more detailed contraceptive advice for women using enzyme inducing drugs, see: **www.nzf.org.nz/nzf_4164.html**

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Oseltamivir (Tamiflu) and Zanamivir (Relenza): Are they actually effective?

Many governments and health authorities throughout the world have stockpiled the neuraminidase inhibitors, oseltamivir and zanamivir in preparation for an influenza pandemic. The decision to stockpile these medicines was based on the belief that they reduced the duration of influenza and prevented hospital admissions and complications, such as pneumonia. The available evidence in 2009, when the decision was made, included only manufacturer-sponsored trials and this evidence was incomplete at that time. New evidence suggests these medicines may not be as effective as previously thought.

New evidence is now available

Oseltamivir

A recent systematic review , published in April, 2014, looked at the available evidence for the efficacy of oseltamivir for influenza illness, including previously unseen complete reports from the original research carried out by the manufacturers Roche and GlaxoSmithKline.[1] The review found that compared to placebo, oseltamivir led to a quicker alleviation of influenza-like symptoms, approximately half a day sooner in adults (from seven days to 6.3 days), but it was unclear if this was the case in children. There was no evidence of a reduction in hospital admissions or serious influenza complications, such as confirmed pneumonia, bronchitis, sinusitis or ear infection in either adults or children. There was also an increased incidence of adverse effects including nausea and vomiting (5% in children and 4% in adults). There was no evidence that oseltamivir prevented person-to-person transmission of influenza.[1]

Zanamivir

The findings for zanamivir were similar.[2] There was a reduction in the time to symptomatic improvement in adults (but not children) by approximately half a day, however, this effect could be attenuated by symptom relief medicines, i.e. symptoms were not better in the treatment arm when compared with symptoms in people in the placebo group taking relief medicines. There was no evidence that zanamavir reduced the risk of complications, particularly pneumonia, or the risk of hospital admission or death. Its use was not associated with a significant risk of harm, but there were occasional reports of bronchospasm.[2]

To sum up: Benefits of oseltamivir and zanamivir appear to be modest

The benefits of both oseltamivir and zanamivir appear to be modest at best, and these benefits must be balanced against the possibility of adverse effects occurring, such as nausea and vomiting.

Treatment for future pandemics?

What this data does not tell us is how well these medicines are likely to perform in a pandemic. The data included in the systematic reviews was for the treatment of seasonal influenza with oseltamivir and zanamivir.[1, 2] More recent observational data collected in 2009 and 2010, during the "swine flu" pandemic suggests that neuraminidase inhibitors are effective for managing people admitted to hospital with severe influenza.[3] These researchers found that neuraminidase inhibitors reduced mortality and that early treatment was associated with a reduction in mortality risk compared with late treatment.[3]

However, others have questioned the robustness of this data, suggesting that the methodology may not have been adequate.[4] It is also suggested that, as influenza is a predictable seasonal threat which poses serious risk to people, particularly those with co-morbidities, adequately designed research is required to fully address whether these medicines are worth the billions of dollars spent on stockpiling them.[4]

Freemantle *et al*[4] concludes: "*Influenza is a predictable threat that occurs every year, and people with co-morbidities face potentially serious consequences as a result. Requiring or facilitating adequately designed research would be in the public interest, and public funding mechanisms have failed in their duty of care towards patients*."

References:

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Emergency contraception: potential problems in overweight women?

Recent evidence suggests that the efficacy of levonorgestrel, a widely used emergency contraceptive pill, is significantly lower in women weighing greater than 70 kg. Medsafe, in conjunction with the Australian Therapeutic Goods Administration (TGA), are continuing to evaluate this efficacy concern and a review is expected soon.[1] There are no specific recommendations from Medsafe or the TGA for action at this time.

The most common form of emergency contraception in New Zealand is levonorgestrel, administered at a single 1.5 g dose. It is estimated that the emergency contraceptive pill (ECP) prevents 85% of pregnancies that may have occurred if taken within the first 48 hours after intercourse.[2] The efficacy drops significantly, to 58%, when used between 48 and 72 hours.[2] The ECP may be used up to 96 hours after unprotected intercourse, but efficacy is uncertain during this time period (between 72 and 96 hours).[3]

There is some evidence that the efficacy of the ECP may be reduced in women who are overweight. Manufacturers of a levonorgestrel-containing ECP available in Europe stated that: "In clinical trials, contraceptive efficacy was reduced in women weighing 75 kg or more, and levonorgestrel was not effective in women who weighed more than 80 kg".[4] This has prompted the European Medicines Agency to start a review of emergency contraceptives, levonorgestrel and ulipristal (not available in New Zealand) to assess whether increased bodyweight and body mass index (BMI) reduce the efficacy of these medicines.[5]

This finding is supported by earlier evidence that the efficacy of levonorgestrel is affected by BMI. Clinical trials found that the risk of pregnancy was doubled in overweight women (BMI 25 – 29.9 kg/m^2) taking levonorgestrel compared with normal or underweight women.[6] Obese women (BMI ≥30 kg/m^2) were four times more likely to become pregnant following use of levonorgestrel as emergency contraception compared with normal or underweight women. Using computer modelling predictive techniques based on clinical trial data, researchers found that pregnancy rates following use of levonorgestrel would be the same as for a woman with a BMI of 26 kg/m^2 who used no emergency contraception, and the limit of efficacy for levonorgestrel ECP was reached at a body weight of 70 kg.[6]

However, researchers noted that there were several limitations to their study, including that:[6]

- The data came from clinical trials that were not designed to explore the effect of body weight or BMI on the efficacy of levonorgestrel ECPs
- The number of women in the studies with a BMI greater than 35 kg/m^2 was small,
- The number of pregnancies in women in this weight range was extremely small

Current advice still stands

Until further evidence is available, and pending review by Medsafe and the TGA, the overall benefit-risk balance of levonorgestrel remains positive and there is no change in advice for women who have had unprotected intercourse. All women, regardless of weight, should be advised to use emergency contraception as soon as possible following unprotected intercourse.[1] This includes using the ECP in women who are overweight or obese, as this is often the most practical method of emergency contraception; however, it is important to explain the possible increased risk of pregnancy. Insertion of an intrauterine device (IUD) within five days can be recommended to women who are particularly concerned, but access to a clinic offering this service may not be available in all areas within the necessary time period.

Another risk factor for emergency contraception failure is further episodes of unprotected intercourse following use of emergency contraception. One study found that women who had unprotected intercourse after using emergency contraception were more than four times as likely to become pregnant compared with those who did not report further unprotected intercourse after using emergency contraception.[6] Therefore, it is important to advise women about ongoing contraceptive needs and recommend barrier methods of contraception after using emergency contraception.

Women prescribed or supplied emergency contraception should be provided with the following additional advice:[3]

- That their next menstrual period may be early or late
- To seek medical attention promptly if any lower abdominal pain occurs; this may indicate an ectopic pregnancy
- To return in three to four weeks if their subsequent menstrual bleed is abnormally light, heavy or brief, or is absent, or if there is any doubt as to whether menstruation has occurred. In these cases, a pregnancy test should be performed at least three weeks after unprotected intercourse.

Copper intrauterine device (IUD) for emergency contraception

Insertion of a copper IUD is more effective than oral levonorgestrel for emergency contraception, if inserted within 120 hours (five days) after unprotected intercourse. If intercourse has occurred more than five days previously, the device can still be inserted up to five days after the earliest likely calculated date of ovulation, regardless of the number of episodes of unprotected intercourse earlier in the cycle.[3]

Some women may consider a copper IUD for emergency contraception, especially if they weigh more than 70 kg and had protected intercourse close to ovulation, and would benefit from the ongoing, long-term contraceptive effect.[7]

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