Dear Dave

Dave and other members of the bpac[nz] team answer your clinical questions

Does the 'seven day rule' still apply with the concomitant use of combined oral contraceptives and all antibiotics?

In June 2006, the American College of Obstetricians and Gynaecologists (ACOG) released a practice bulletin on the use of hormonal contraception in women with coexisting medical conditions. This bulletin has cast some doubt over whether it is valid for GPs to advise their patients taking oral contraceptives that they need to use other methods of contraception for the duration of antibiotic treatment and the following seven days.

"Although there have been many anecdotal reports of oral contraceptive failure in women taking concomitant antibiotics, pharmacokinetic evidence of lower serum steroid levels exists only for rifampicin. Because oral contraceptive steroid concentrations are strikingly reduced in women concomitantly taking rifampicin, such women should not rely on combination oral contraceptives, progestin-only oral contraceptives or implants for contraceptive protection". ACOG[1]

The fact that rifampicin can cause oral contraceptive failure is unequivocal due to enzyme induction, increased oestrogen metabolism and resultant reduced plasma oestrogen concentrations. Most other antibiotics have been reported to be associated with oral contraceptive failure, but as stated in the ACOG Practice Bulletin, clinical studies have not demonstrated that antibiotics (other than rifampicin) decrease serum steroid concentrations.

There is a theoretical basis for an interaction in that antibiotics reduce gut flora which are responsible for increasing the reabsorption of oestrogens from the GI tract. Oestrogens are metabolised in the liver and conjugated with glucuronide, which is water soluble and can be excreted in the bile. Under normal gut flora conditions, bacteria cleave this conjugate and free up oestrogen, which can then be reabsorbed (enterohepatic recycling). Although the theory is not backed up by evidence from clinical studies, an interaction cannot be completely ruled out as in some women enterohepatic recycling may be crucial, in maintaining adequate oestrogen plasma concentrations. Clinical studies may also not represent the situation in practice where antibiotics or the underlying illness may cause diarrhoea or vomiting, which are known to reduce the effectiveness of oral contraceptives.

Bearing in mind that there is a background failure rate associated with oral contraception, it is not possible to prove that an antibiotic given concurrently is causative or contributory to a case of failure. Although an interaction and resultant contraceptive failure is probably extremely unlikely, the possibility cannot be completely excluded.

On moral and ethical grounds most authorities continue to sanction the cautious approach and continue to recommend the seven day rule.

Reference

Stockley's Text Book of Drug Interactions 2007.

1. ACOG Practice Bulletin. Clinical Management Guidelines for Obstetricians and Gynecologists. Number 73, June 2006.

If you have a clinical question email it to
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Serotonin toxicity: "Is combining Reductil with tricyclic antidepressants really such a no-no or are the drug companies just being defensive over the unlikely occurrence of serotonin syndrome?"

Bob Buckham from the Christchurch Drug Information Centre was asked if he had come across this question in practice. His advice was as follows:

Serotonin toxicity

Sibutramine and amitriptyline work by inhibiting the reuptake of serotonin and noradrenaline. Concurrent use of these drugs is actively discouraged because of the potential for serotonin toxicity (which may range from mild symptoms, such as diarrhoea or sweating, through to coma and death). Furthermore, TCAs may cause weight gain and both agents lower the seizure threshold.

The risk would be (theoretically) greater with tertiary amine TCAs (compared to secondary amine) as they are more serotonergic. So it could be argued that nortriptyline might be 'safer' and less likely to cause serotonin toxicity than amitriptyline or imipramine. The concurrent use of sibutramine and clomipramine should definitely be avoided as this TCA has potent serotonerigic properties.

Similarly, it would be a dose-dependent effect, therefore the relevance of dose needs to be considered. However overall we try to discourage the combination and suggest trying orlistat (Xenical) first-line. If that is not an option then we would need to seriously weigh risk versus benefit and monitor carefully. We also make the same recommendation if the patient is taking an SSRI or a monoamine oxidase inhibitor (MAOI).

Instead of serotonin 'syndrome', we try to refer to it as serotonin toxicity, as most people usually know that the 'syndrome' is actually only rarely reported – so they tend to disregard it. Whereas 'toxicity' suggests a range of issues from mild symptoms, like diarrhoea and sweating, many probably wouldn't think to associate it with serotonin toxicity, to the serious signs like tremor, seizures, coma and death (the 'syndrome').

In summary, like other combinations which have the potential for toxicity (e.g. SSRIs + TCAs) the combination of sibutramine and a TCA may be uneventful in many people. The risk of an interaction is probably lower with low doses of nortriptyline than with other TCAs at high doses.

Concurrent use is governed by appreciation of risk versus benefit, recognition of the general advice against its use and the need to closely monitor patients if the combination is used.

Further reading about serotonin toxicity
http://snipurl.com/1ps35

Who is Dave?

Pharmaceutical Programme Manager Dave Woods is a graduate of Manchester University (B.Sc. [Hons]) and the University of Otago (MPharm). Dave has extensive experience in hospital pharmacy, drug information, rational use of drugs and quality assurance. He has published on a range of subjects and holds editorial positions for several international journals.

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