RGH Pharmacy E-Bulletin

Volume 44 (6): November 14, 2011

A joint initiative of the Patient Services Section and the Drug and Therapeutics Information Service of the Pharmacy Department, Repatriation General Hospital, Daw Park, South Australia. The RGH Pharmacy E-Bulletin is distributed in electronic format on a weekly basis, and aims to present concise, factual information on issues of current interest in therapeutics, drug safety and cost-effective use of medications.
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Warfarin/antibiotic interactions

While alternative oral anticoagulant drugs such as dabigatran have recently been developed, warfarin is currently still the most commonly used and only PBS-listed oral anticoagulant in Australia for the prevention and treatment of thromboembolism in patients with mechanical heart valves, atrial fibrillation and deep vein thrombosis or pulmonary embolus. Warfarin exerts its therapeutic action as a vitamin K antagonist, lowering the amount of vitamin K available for the production of important clotting factors.

Warfarin has a narrow therapeutic index requiring regular monitoring due to the potential for variability in response, altered vitamin K status and drug interactions. As variability in response to warfarin can have major consequences, it is important to be aware of potential factors which can influence an individual's coagulation status. Numerous medications are known to potentially influence a person's coagulation (measured by the international normalised ratio or INR), including antibiotics.

Antibiotics have the potential to interact with a person's INR in multiple ways, including disruption of intestinal flora and the intestinal synthesis of vitamin K. Antibiotics can also interfere with the metabolism of warfarin by influencing the cytochrome P450 enzymes responsible for the metabolism of warfarin (via induction or inhibition). Warfarin is manufactured as a racemic mixture of (R) and (S) enantiomers, and the CYP 450 enzyme 2C9 (which metabolises the more biologically active S-enantiomer) can be affected by antibiotics such as sulphamethoxazole (a known CYP 2C9 inhibitor).

In general, patients who are systemically unwell and require antibiotic therapy may be more susceptible to increased sensitivity to warfarin and the potential for over-anticoagulation due to decreased oral intake of vitamin K. It has also been suggested that febrile illness may increase the breakdown of vitamin K dependent clotting factors by producing a hypermetabolic state. A case-control study which looked at hospitalisations for upper gastrointestinal haemorrhage during warfarin therapy associated with antibiotics used for the management of urinary tract infections found that bleeding cases were almost four times more likely than controls to have recently been treated with the combination trimethoprim/sulphamethoxazole during the preceding fourteen days. Ciprofloxacin was also associated with an increased risk (possibly due to inhibition of CYP 1A2 which metabolises the R-isomer of warfarin) however no significant increased risk was associated with amoxicillin, ampicillin, nitrofurantoin or norfloxacin. Although this was a case-control study with inherent limitations, the interaction between antibiotics and warfarin has been reported in a number of case reports.

When prescribing antibiotics for a person on warfarin therapy, the potential for significant drug interactions should be considered. Precautions that may be beneficial include increased INR testing, especially when starting or stopping any antibiotic, and increased monitoring for any signs of over-anticoagulation or bleeding. While some sources recommend a pre-emptive reduction in warfarin dosage before commencement of antibiotics known to interact, this approach has also been discouraged by others due to the potential for under dosing and sub-therapeutic INR results. Due to the variability in response and numerous influencing factors, concurrent warfarin therapy and antibiotics may be best managed by increased clinical care and monitoring, taking into account the individual's risk factors for bleeding or clotting.

Acknowledgment – This E-Bulletin is based on work by Ellise Liew, Clinical Pharmacist, RGH

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