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BY FAX
21 Jun 2024

The President
College of Surgeons of Hong Kong
(Fax Number: 2515 3198)

Dear Sirs,

Warfarin: be alert to the risk of drug interactions with tramadol

Your attention is drawn to the United Kingdom Medicines and Healthcare products Regulatory Agency's (MHRA) announcement that warfarin and tramadol together can cause harmful drug interactions, which can raise the International Normalised Ratio (INR), and result in severe bruising and bleeding, which in some patients could be fatal.

The MHRA has received a Coroner's report following the death of a patient who died from a bleed on the brain, following concurrent treatment with warfarin and tramadol. Taking warfarin and tramadol together may increase a patient's INR and increase the risk of bleeding. The Coroner raised concerns that the interaction between warfarin and tramadol was not well known and emphasised the need to highlight this interaction to healthcare professionals.

Warfarin is a coumarin-derived vitamin K antagonist used for prevention and treatment of blood clots. It is used to prevent embolisation in rheumatic heart disease and, atrial fibrillation and after insertion of prosthetic heart valves. Warfarin is also used in the prevention and treatment of venous thrombosis and pulmonary embolism and treatment of transient ischaemic attacks.

Warfarin has a low therapeutic index, which means care is required when taking co-prescribed medicines due to the possibility of interactions that could lead to an increased risk of bleeding.

The product information for warfarin advises that healthcare professionals should refer to the product information of any new concomitant medicines for specific guidance on use with warfarin and whether a dose adjustment or therapeutic monitoring is required. The product information will be updated to include the interaction in due course.

Tramadol is a non-selective opioid analgesic, which acts as an agonist at the mu, delta and kappa opioid receptors. Section 4.5 of the tramadol Summary of Product Characteristics states that caution should be exercised during concomitant treatment with coumarin derivatives such as warfarin due to reports of increased INR with major bleeding and bruising in some patients. While the risk of major bleeding with warfarin treatment is rare, the risk may be increased with concurrent use of tramadol.

Advice for healthcare professionals:

- Warfarin is a coumarin-derived vitamin K antagonist which has a low therapeutic index, so continue to exercise caution when co-prescribing warfarin with other drugs, to minimise the risk of drug interactions.
- Ask patients about all the medicines that they are currently taking.
- Be aware of the risk of increased INR when warfarin and tramadol are used together, with a risk of major bruising and bleeding which could be life-threatening.
- Consult the product information of any new concomitant therapy for specific guidance on use with warfarin and consider whether warfarin dose adjustment is required.
- Consider whether additional monitoring of INR is required when starting tramadol or another concomitant medicine.
- Ensure patients are aware of the need to seek medical treatment should they notice the signs of a major bleeding event.
- Caution should also be taken if tramadol is co-prescribed with other coumarin-derived anticoagulants such as acenocoumarol.

Please refer to the following website in MHRA for details:
https://www.gov.uk/drug-safety-update/warfarin-be-alert-to-the-risk-of-drug-interactions-with-tramadol

In Hong Kong, there are 4 registered pharmaceutical products containing warfarin and 42 products containing tramadol. All products are prescription-only medicines. So far, with regard to warfarin, the Department of Health (DH) has received 15 cases of adverse drug reaction, of which 2 cases were reported as drug interaction. With regard to tramadol, the DH has received 9 cases of adverse drug reaction, but these cases were not related to drug interaction. In light of the above MHRA's announcement, the matter will be discussed by the Registration Committee of the Pharmacy and Poisons Board.

Please note that this letter serves as a means for the DH to communicate important new safety information about registered pharmaceutical products with healthcare professionals in Hong Kong and is not intended to serve as guidelines or to replace professional clinical judgement. Healthcare professionals are advised to balance the risk of possible adverse effects against the benefit of treatment.

Please report any adverse events caused by drugs to the Clinical Trials and Pharmacovigilance Unit of the DH (tel. no.: 2319 2920, fax: 2319 6319 or email: adr@dh.gov.hk). For details, please refer to the website at Drug Office under "ADR Reporting": http://www.drugoffice.gov.hk/adr.html. You may wish to visit the Drug Office's website for subscription and browsing of "Drug News" which is a monthly digest of drug safety news and information issued by Drug Office.

Yours faithfully,

P.P. (Terence MAN)
for Assistant Director (Drug)