Drug Safety Update

Latest advice for medicines users

The monthly newsletter from the Medicines and Healthcare products Regulatory Agency and its independent advisor the Commission on Human Medicines

Volume 9, Issue 12, **July 2016**

Contents

The Medicines and Healthcare products Regulatory Agency is the government agency which is responsible for ensuring that medicines and medical devices work, and are acceptably safe.

The Commission on Human Medicines gives independent advice to ministers about the safety, quality, and efficacy of medicines. The Commission is supported in its work by Expert Advisory Groups that cover various therapeutic areas of medicine.

NICE accredited
www.nice.org.uk/accreditation

The MHRA is accredited by NICE to provide Drug Safety Update. Further information can be found on the NICE Evidence Search portal: www.evidence.nhs.uk/

Cases of calciphylaxis have been reported in patients taking warfarin, including those with normal renal function. Calciphylaxis is a very rare but serious condition involving vascular calcification and skin necrosis that is most commonly observed in patients with known risk factors such as end-stage renal disease. If calciphylaxis is diagnosed, appropriate treatment should be started and consideration should be given to stopping treatment with warfarin (page 2).

Finally this month, we are highlighting a recent MHRA medical device alert that N-acetylcysteine may interfere with assays from Siemens ADVIA Chemistry and Dimension/Dimension Vista instruments, leading to false-low biochemistry test results. Further information is on page 4.

drugsafetyupdate@mhra.gsi.gov.uk

Warfarin: reports of calciphylaxis

Calciphylaxis is a very rare but serious condition causing vascular calcification and skin necrosis.

Advice for healthcare professionals:

- calciphylaxis is a very rare but serious condition that is most commonly observed in patients with known risk factors such as end-stage renal disease
- cases have been reported in patients taking warfarin, including those with normal renal function, and evidence suggests that on rare occasions warfarin use might lead to calciphylaxis
- if calciphylaxis is diagnosed, appropriate treatment should be started and consideration should be given to stopping treatment with warfarin

Warfarin is an oral anticoagulant. It is a vitamin K antagonist that acts by inhibiting the formation of active clotting factors II, VII, IX, and X.

Risk of calciphylaxis

Calciphylaxis is a very rare but serious condition that causes vascular calcification and cutaneous necrosis. The mortality rate is high. It is also known as calcific uremic arteriolopathy.

The condition is most commonly observed in patients with end-stage renal disease on dialysis, or in those with known risk factors such as: protein C or S deficiency; hyperphosphataemia; hypercalcaemia; or hypoalbuminaemia.

Cases of calciphylaxis have been reported in patients taking warfarin. Pre-existing renal disease was commonly reported in cases, but some reports noted normal renal function.

An EU-wide review of relevant evidence recently concluded that there is a reasonable possibility that on rare occasions warfarin use might lead to calciphylaxis. The product information for warfarin will be updated with the above advice. The patient information leaflet will also be updated to warn patients of the risk of calciphylaxis, with advice to consult their doctor if they develop a painful skin rash.

Potential mechanisms

Calciphylaxis is poorly understood and the exact pathogenesis is unknown. Calciphylaxis and warfarin-induced skin necrosis can present with similar clinical findings, but can be differentiated by histopathology.[1] The mechanism could be mediated through the matrix Gla protein, which is a vitamin-K-dependent protein involved in the inhibition of calcification. Warfarin inhibits Gla protein and may therefore promote vascular calcification in susceptible individuals.[2]

1 Nazarian RM et al. Warfarin-induced skin necrosis. Journal of the American Academy of Dermatology 2009; 61: 325–32.
2 Saifan C et al. Warfarin-induced calciphylaxis: a case report and review of literature. International Journal of General Medicine 2013; 6: 665–69.

Article citation: Drug Safety Update volume 9 issue 12 July 2016: 1

Citalopram: suspected drug interaction with cocaine; prescribers should consider enquiring about illicit drug use

Possible illicit drug use should be considered when prescribing medicines that have the potential to interact adversely.

Suspected drug interaction between citalopram and cocaine

We received a Coroner's report that raised concerns about a suspected drug interaction between citalopram and cocaine after the death of a man due to subarachnoid haemorrhage.

The case was discussed by the UK Commission on Human Medicine's Pharmacovigilance Expert Advisory Group. There are plausible mechanisms for an interaction between cocaine and citalopram that could lead to subarachnoid haemorrhage, including hypertension related to cocaine and an additive increased bleeding risk in combination with citalopram.

Enquiring about potential illicit drug use

Guidance from the General Medical Council states that, together with the patient, healthcare professionals should make an assessment of the patient's condition before deciding to prescribe a medicine. The professional must have, or take, an adequate history, which considers recent use of other medicines—including non-prescription medicines, herbal medicines, illegal drugs, and medicines purchased online.

In particular, when prescribing selective serotonin reuptake inhibitors (SSRIs), prescribers are reminded to enquire about cocaine use when considering drug–drug interactions and the need to avoid concurrent use of multiple serotonergic drugs.

In light of this Coroner's case, we remind prescribers to note the potential increased risk of bleeding when citalopram is prescribed to patients who are taking cocaine.
More generally, the possibility of illicit drug use and interactions should be considered when prescribing any medicines that have the potential to interact adversely.

Possible interactions with illicit drugs should also be considered in patients who present with suspected adverse reactions to a medicine. Remember that these can be reported to us on a Yellow Card.

Article citation: Drug Safety Update volume 9 issue 12 July 2016: 2

N-acetylcysteine: risk of false-low biochemistry test results due to interference with Siemens assays

N-acetylcysteine may interfere with assays from Siemens ADVIA Chemistry and Dimension/Dimension Vista instruments, leading to false-low biochemistry test results.

Advice for healthcare professionals:

Professionals who are treating patients with N-acetylcysteine for paracetamol overdose should establish whether Siemens ADVIA Chemistry and Dimension/Dimension Vista instruments are used for laboratory testing of biochemistry and, if so, should:

- do venipuncture and blood sampling before N-acetylcysteine administration; there is a risk of false low biochemistry test results and potential misinterpretation of physiological status if done during or immediately after administration
- state if a patient is receiving N-acetylcysteine when requests for biochemistry tests (eg, cholesterol, uric acid, lactate) include any affected assays from these instruments

False low biochemistry test results may occur when testing samples drawn from patients receiving N-acetylcysteine for paracetamol overdose due to interference with the reaction assays of these Siemens instruments.

Further information, including a full list of affected assays, can be found in a medical device alert sent 22 June 2016.

Adverse incidents can be reported via: the Yellow Card Scheme in England and Wales; the Northern Ireland Adverse Incident Centre; or Health Facilities Scotland.

Article citation: Drug Safety Update volume 9 issue 12 July 2016: 3

Letters sent to healthcare professionals in June 2016

On 20 June 2016, a letter was sent to healthcare professionals about risks of viral reactivation and pulmonary hypertension associated with Thalidomide Celgene.

Article citation: Drug Safety Update volume 9 issue 12 July 2016: 4