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 10 Issue 6 January 2017

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/

This month, we have 2 articles for professionals who manage patients with chronic hepatitis C. The first article advises that rapid reduction in hepatitis C viral load during treatment with direct-acting antiviral interferon-free regimens may lead to increased replication of hepatitis B virus in co-infected patients. Therefore, all patients with hepatitis C who are starting therapy with these antivirals should be screened for hepatitis B infection, and should be monitored and managed for co-infection according to current clinical guidelines (page 2).

The second article is about changes in liver function due to treatment with direct-acting antivirals for chronic hepatitis C infection, which may result in fluctuations of INR values, in patients also taking vitamin K antagonists (eg, warfarin). In these patients, INR should be monitored closely and, if necessary, anticoagulant therapy adjusted (page 3).

A review of the evidence from clinical trials and postmarketing cases has suggested a causal association between suicidal thoughts or suicidal behaviour and apremilast—a treatment for severe chronic plaque psoriasis or active psoriatic arthritis in adults. Treatment should be stopped if patients have new psychiatric symptoms or if existing symptoms worsen. The balance of benefits and risks of starting or continuing treatment should be carefully assessed in patients with a history of psychiatric symptoms, or in those who are taking other medicines likely to cause these symptoms. Patients should be advised to inform a healthcare professional if they notice changes in their mood—see page 4.

Finally this month, we summarise the Commission on Human Medicine's review of intravenous N-acetylcysteine (NAC) for treatment of paracetamol overdose. As a result of the review, prescribing information is being updated to advise that continued treatment with NAC beyond 21 hours may be necessary depending on the clinical evaluation of the individual patient (page 5).

drugsafetyupdate@mhra.gsi.gov.uk

© Crown Copyright 2017

Direct-acting antiviral interferon-free regimens to treat chronic hepatitis C: risk of hepatitis B reactivation

All patients should be screened for hepatitis B before starting treatment for chronic hepatitis C with direct-acting antiviral interferon-free regimens. Patients who are co-infected with hepatitis B and C viruses are at risk of hepatitis B reactivation, and should be monitored and managed according to current clinical guidelines.

Advice for healthcare professionals:

- rapid reduction in hepatitis C viral load during treatment with direct-acting antiviral interferon-free regimens may lead to increased replication of hepatitis B virus in co-infected patients
- all patients with hepatitis C who are starting therapy with direct-acting antiviral interferon-free regimens should be screened for hepatitis B infection, and should be monitored and managed for co-infection according to current clinical guidelines

Advice for professionals to give to patients:

- patients should be advised to inform their doctor or pharmacist if they have a current or previous infection with hepatitis B virus if they are prescribed direct-acting antiviral interferon-free regimens for hepatitis C
- patients should be advised that they may be monitored more closely if they have a current or previous infection with hepatitis B virus

Direct-acting antivirals used as part of interferon-free regimens for the treatment of chronic hepatitis C infection are: daclatasvir (Daklinza▼); dasabuvir (Exviera▼); ombitasvir, paritaprevir, ritonavir (Viekirax▼); sofosbuvir (Sovaldi▼); ledipasvir with sofosbuvir (Harvoni▼); and simeprevir (Olysio▼).

Cases of a return of previously inactive hepatitis B infection have been reported in patients treated with direct-acting antiviral interferon-free regimens who were infected with hepatitis B and C viruses. An EU-wide review has confirmed that there is a risk of hepatitis B reactivation in patients co-infected with hepatitis B and C viruses who are initiated on these antivirals for chronic hepatitis C.

The benefits of treatment with direct-acting antiviral interferon-free regimens for chronic hepatitis C continue to outweigh the risks of reactivation of hepatitis B infection. However, all patients should be screened for hepatitis B before initiation of treatment with hepatitis C direct-acting antiviral interferon-free regimens. Co-infected patients should be monitored and managed according to current clinical guidelines.

Any suspected adverse reactions to direct-acting antivirals should be reported to us on a Yellow Card.

Article citation: Drug Safety Update volume 10 issue 6, January 2017: 1.

© Crown Copyright 2017

Direct-acting antivirals to treat chronic hepatitis C: risk of interaction with vitamin K antagonists and changes in INR

INR should be monitored closely during treatment of chronic hepatitis C with direct-acting antivirals in patients also receiving vitamin K antagonists (eg, warfarin), because of possible changes in liver function during treatment.

Advice for healthcare professionals:

- changes in liver function due to treatment with direct-acting antivirals for chronic hepatitis C infection may result in fluctuations of INR values in patients taking vitamin K antagonists
- in these patients, INR should be monitored closely and, if necessary, anticoagulant therapy adjusted

Advice for professionals to give to patients:

- patients should be advised to inform their doctor or pharmacist that they are taking warfarin or other similar medicines called vitamin K antagonists used to thin the blood if they are prescribed direct-acting antivirals
- patients who are receiving vitamin K antagonists should be advised that during treatment with direct-acting antivirals for chronic hepatitis C, they may have more-regular blood tests to check how well their blood can clot

Direct-acting antivirals for the treatment of chronic hepatitis C infection include: boceprevir (Victrelis); daclatasvir (Daklinza▼); dasabuvir (Exviera▼); ombitasvir, paritaprevir, ritonavir (Viekirax▼); sofosbuvir (Sovaldi▼); ledipasvir with sofosbuvir (Harvoni▼); and simeprevir (Olysio▼). Vitamin K antagonists are used as anticoagulant medicines, and include warfarin and acenocoumarol.

A Europe-wide review of the use of concomitant vitamin K antagonists and direct-acting antivirals for chronic hepatitis C has identified that changes in INR occur during treatment. Changes in liver function secondary to hepatitis C treatment are thought to affect the efficacy of vitamin K antagonists.

The benefits of treatment with direct-acting antivirals for chronic hepatitis C continue to outweigh the risks of an interaction with vitamin K antagonists. However, INR values should be monitored closely in patients receiving this concomitant treatment because changes in liver function may affect INR values and necessitate adjustment of anticoagulant therapy.

Any suspected adverse reactions to direct-acting antivirals, vitamin K antagonists, or any other medicines should be reported to us on a Yellow Card.

Article citation: Drug Safety Update volume 10 issue 6, January 2017: 2.

© Crown Copyright 2017

Apremilast (Otezla ▼): risk of suicidal thoughts and behaviour

There is an increased risk that some patients may experience psychiatric symptoms with apremilast, including depression and suicidal thoughts. Stop treatment if patients have new psychiatric symptoms or if existing symptoms worsen.

Advice for healthcare professionals:

- apremilast is associated with an increased risk of psychiatric symptoms, including depression, suicidal thoughts, and suicidal behaviours
- suicidal thoughts and behaviour, including completed suicide, have been reported in patients with or without a history of depression
- carefully assess the benefits and risks of starting or continuing treatment in patients with a history of psychiatric symptoms, or in those who are taking other medicines likely to cause psychiatric symptoms
- stop treatment if patients experience new psychiatric symptoms or if existing symptoms get worse
- advise patients to inform a healthcare professional if they notice changes in their mood

Apremilast (Otezla▼) is a phosphodiesterase-type-4 inhibitor for the treatment of moderate to severe chronic plaque psoriasis or active psoriatic arthritis in adults who have not responded to other systemic treatments.

Risk of suicidal thoughts and behaviour

Depression, suicidal thoughts, and suicidal behaviours are more common in patients with psoriasis or psoriatic arthritis than in the general population. Clinical trials and postmarketing experience (including reports to the Yellow Card scheme) have recorded serious psychiatric symptoms, including depression, suicidal thoughts, and suicidal behaviours. Suicidal thoughts and behaviours have been reported in patients with no previous history of depression.

A review of the evidence from clinical trials and postmarketing cases has suggested a causal association between apremilast and suicidal thoughts and suicidal behaviour. These events are reported to occur uncommonly, with an estimated frequency of between 1 in 1000 to 10 in 1000 patients taking apremilast.

Reporting of suspected adverse reactions

Suspected adverse reactions should be reported to us on a Yellow Card.

Further information

Letter sent to healthcare professionals, November 2016

Article citation: Drug Safety Update volume 10 issue 6, January 2017: 3.

© Crown Copyright 2017

Intravenous N-acetylcysteine (NAC) for paracetamol overdose: reminder of authorised dose regimen; possible need for continued treatment with NAC

The authorised dose regimen for N-acetylcysteine (NAC) in paracetamol overdose is 3 consecutive bags given intravenously over 21 hours. Prescribing information is being updated to advise that continued treatment with NAC may be necessary depending on clinical evaluation of the individual patient.

Advice for healthcare professionals:

- the authorised posology for intravenous N-acetylcysteine (NAC) in the treatment of paracetamol overdose is 3 consecutive intravenous infusions
    - first infusion: initial loading dose of 150 mg/kg bodyweight over 1 hour
    - second infusion: 50 mg/kg over the next 4 hours
    - third infusion: 100 mg/kg over the next 16 hours

- the patient should receive a total dose of 300 mg/kg bodyweight over a 21-hour period. A ceiling weight of 110 kg should be used when calculating the dose for obese patients

- continued treatment with NAC (given at the dose and rate as used in the third infusion) may be necessary depending on the clinical evaluation of the individual patient

Intravenous NAC is the antidote to treat paracetamol overdose and is virtually 100% effective in preventing liver damage when given within 8 hours of the overdose. After this time efficacy falls substantially, affording only a very limited window of time in which to successfully prevent serious hepatotoxicity.

Simplified guidance on the treatment of paracetamol overdose with NAC was implemented in September 2012, after an evidence-based review by the Commission on Human Medicines (CHM).

Since 2012, data for an off-label shortened 2-bag regimen for NAC to treat paracetamol overdose have been published from the Scottish and Newcastle Antiemetic Pre-treatment for paracetamol poisoning (SNAP) study.[1] CHM have reviewed these findings and, as part of their review, also looked at the safety profile of NAC since the 2012 guidance was implemented.

CHM concluded that there was insufficient evidence of efficacy to add information about the off-label shortened 2-bag dose regimen used in the SNAP study to the product information for NAC.

The pattern of potential adverse drug reactions associated with NAC is well established, and no new safety issues have been identified since the 2012 guidance. The authorised NAC product information reflects the safety profile. CHM concluded that the benefits of the authorised 3-bag dose regimen continue to outweigh the risks. As with all medicines, suspected adverse reactions should continue to be reported to us on a Yellow Card.

1. Bateman DN, et al. Reduction of adverse effects from intravenous acetylcysteine treatment for paracetamol poisoning: a randomised controlled trial. Lancet 2014; 383: 697–704.

© Crown Copyright 2017

Potential need to continue treatment: prescribing update

As a result of the review, in line with current clinical guidance, prescribing information for NAC is being updated to advise that continued treatment with NAC beyond 21 hours may be necessary depending on the clinical evaluation of the individual patient.

Article citation: Drug Safety Update volume 10 issue 6, January 2017: 4.

Letters sent to healthcare professionals in December 2016

In December 2016, the following letters were sent to relevant healthcare professionals:

- Levetiracetam (Keppra) 100 mg/mL: risk of medication errors
- Ammonaps (sodium phenylbutyrate): only for use when there is no alternative treatment

Article citation: Drug Safety Update volume 10 issue 6, January 2017: 5.

© Crown Copyright 2017