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 11 Issue 2 September 2017

Contents

The Medicines and Healthcare products Regulatory Agency (MHRA) is the government agency 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.

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This month, we have updated advice on minimising risk of bleeding events with miconazole oral gel in patients taking warfarin (page 2).

Over-the-counter miconazole oral gel from pharmacies is contraindicated in patients taking warfarin. If you plan to prescribe miconazole oral gel in a patient on warfarin, ensure that you monitor and titrate the anticoagulant effect carefully.

In the second article, we highlight serious cardiac adverse reactions in people who have taken large or very large doses of loperamide (page 4). As for all medicines, pharmacists should remind patients not to take more than the recommended dose on the label.

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Miconazole (Daktarin): over-the-counter oral gel contraindicated in patients taking warfarin

Patients taking warfarin should not use over-the-counter miconazole oral gel (Daktarin). If you plan to prescribe miconazole oral gel in a patient on warfarin, you should closely monitor them and advise that if they experience any sign of bleeding, they should stop miconazole oral gel and seek immediate medical attention.

Advice for healthcare professionals:

- bleeding events, some with fatal outcome, have been reported with use of miconazole oral gel by patients on warfarin
- patients taking warfarin should not use over-the-counter miconazole oral gel available from pharmacies
- if the concomitant use of miconazole oral gel with an oral anticoagulant such as warfarin is planned, exercise caution and ensure that you monitor and titrate the anticoagulant effect carefully
- advise patients taking prescription-only miconazole oral gel and warfarin that if they experience signs of over-anticoagulation, such as sudden unexplained bruising, nosebleeds, or blood in urine, they should stop using miconazole and seek immediate medical attention

Review of interaction

The antifungal drug miconazole inhibits several P450 isozymes, including CYP2C9, which can heighten the anticoagulant effect of warfarin and lead to an increase in international normalised ratio (INR) values (and subsequent bleeding complications).

The potential for an interaction between miconazole and warfarin is documented in published literature, with articles describing case reports of interactions dating from the 1980s to 2016.[1–3] Because of this, warnings are given in the summaries of product characteristics about the potential for drug interactions between anticoagulants/warfarin and azole antifungals (of which miconazole is one) and the need for the anticoagulant effect to be carefully monitored.

In March 2016, the Medicines and Healthcare products Regulatory Agency (MHRA) received a Prevention of Future Deaths (regulation 28) report from a coroner regarding the death of a patient from intracerebral haemorrhage. The coroner raised concerns about the risks for a drug interaction between miconazole oral gel and warfarin, and a possible lack of awareness of the interaction among healthcare professionals.

In response to this report, the MHRA initiated a review of available data about this interaction. The Commission on Human Medicines was asked to advise on whether measures were needed to minimise risk to patients.

1. Stockley I. Drug interaction with coumarin derivative anticoagulants. BMJ 1982; 285: 1044–45.
2. Ariyaratnam S, et al. Drug points: Potentiation of warfarin anticoagulant activity by miconazole oral gel. BMJ 1997; 314: 349.
3. Filmer S. Warfarin and oral miconazole: a major interaction overlooked in practice. The Pharmaceutical Journal, 1 April 2012.

While further measures were being considered, an article in Drug Safety Update cautioned that miconazole oral gel is systemically absorbed and can enhance the anticoagulant effects of warfarin, potentially causing bleeding events.

Since the article was published in June 2016, we have received 25 Yellow Card reports, bringing the total possible drug interactions with miconazole and warfarin to 175. The most common events reported have been increased INR (135 reports), contusion (23 reports), and haematuria (19 reports). A fatal outcome was reported in 3 cases.

Our review concluded that to minimise potential risks to patients, the following changes should be implemented:

- contraindication of warfarin use for over-the-counter miconazole oral gel, which will also be clearly reflected on the outer carton and on the tube
- more prominent and explicit warnings and information about the potential for an interaction between miconazole oral gel and warfarin, and risks associated with concomitant use of these products, throughout the summary of product characteristics and the patient information leaflet, and, for over-the-counter miconazole oral gel, the label (tube and carton)

Background

In the UK, miconazole oral gel is recommended as first-line treatment for localised or mild oral candida (oral thrush) infection in children (aged over 4 months) and adults.

Two miconazole oral gel products are authorised in the UK:

- Daktarin Oral Gel is classified as a prescription-only medicine (POM)
- Daktarin Oral Gel Sugar Free 2% is classified as a pharmacy (P) medicine available without prescription but only from pharmacies, supplied by or under the supervision of a pharmacist

Warfarin is an oral anticoagulant that has been widely used since the 1950s for prophylaxis of thromboembolic events. Daily dose depends on individual requirements and patients receiving therapy require regular coagulation tests.

Reporting of suspected adverse reactions

Suspected drug interactions between miconazole and anticoagulants such as warfarin should be reported to us on a Yellow Card.

Article citation: Drug Safety Update volume 11 issue 2, September 2017: 1.

Loperamide (Imodium): reports of serious cardiac adverse reactions with high doses of loperamide associated with abuse or misuse

There have been reports of cardiac events including QT prolongation, torsades de pointes, and cardiac arrest in patients who have taken high or very high doses of loperamide as a drug of abuse or for self-treatment of opioid withdrawal.

Advice for healthcare professionals:

- serious cardiovascular events (such as QT prolongation, torsades de pointes, and cardiac arrest), including fatalities, have been reported in association with large overdoses of loperamide
- healthcare professionals are reminded that if symptoms of overdose occur, naloxone can be given as an antidote
- since the duration of action of loperamide is longer than that of naloxone (1–3 hours), repeated treatment with naloxone might be indicated; patients should be monitored closely for at least 48 hours to detect possible CNS depression
- as for all medicines, pharmacists should remind patients not to take more than the recommended dose on the label
- report all suspected adverse reactions, including those associated with abuse or misuse, to the Yellow Card Scheme

Review of cardiovascular adverse reactions associated with loperamide

Loperamide has been on the market since the 1970s and is considered very safe when used in accordance with instructions on the label and in the patient information leaflet.

A European review of worldwide spontaneous reports identified 19 cases suggestive of cardiac rhythm disorders associated with loperamide abuse and misuse. In all cases, there was evidence of intentional high doses being taken for unapproved indications.

In 13 of the 19 reports, QT prolongation or torsades de pointes were recorded with daily dosages ranging from 40–80 mg up to 800 mg (the recommended maximum daily dose is 16 mg).

Of the other 6 reports, one described syncope and irregular heart beat (daily dose 400–600 mg), one described cardiac arrest with a rhythm of pulseless electrical activity (daily dose 400–800 mg), one described ventricular dysrhythmia (daily dose 400 mg), and one described asystole and death (chronic massive overdose). Two reports did not provide specific information on cardiac rhythm disorders or dose, with one describing syncope and death and one loss of consciousness.

As a result of the European review, all manufacturers of loperamide products have been asked to update their product information to include warnings of cardiac events associated with high doses. The patient leaflet will also be updated to warn patients never to take more than the recommended amount.

UK data

We have received 16 UK Yellow Card reports of cardiac-related adverse events associated with loperamide; however, most of these cases date back to the 1970s and 1980s and provide few details. We are aware that adverse events associated with misuse of drugs are under-reported.

Two of 16 reports list doses higher than the licenced daily limit. Dose was not recorded in 10 of the 16 cases. Of 4 cases reporting doses within the licensed range, only one report was not associated with anaphylaxis or underlying cardiac disease.

Of the 16 cardiac-related adverse events described by Yellow Cards, 5 were fatal. One death was suspected to be due to a large overdose of loperamide, whereas 4 deaths were associated with underlying cardiac disease or anaphylaxis**.**

Mechanism of adverse reaction

Non-clinical data offer a biologically plausible mechanism for the reaction (QT prolongation and arrhythmias caused by potassium channel (hERG) inhibition at high doses). At extremely high concentrations, loperamide also has the potential to slow cardiac conduction via inhibition of sodium channels, and produce conduction arrhythmias.

Background

Loperamide is a synthetic opioid that inhibits gut motility by binding to opiate receptors in the gut wall and may also reduce gastrointestinal secretions, resulting in improvement in diarrhoea symptoms. Loperamide also increases the tone of the anal sphincter.

Loperamide is indicated for the symptomatic treatment of acute diarrhoea. In the UK, loperamide (brand name Imodium) is available on general sale (maximum daily dose 12 mg) and from pharmacists (maximum daily dose 16 mg).

Further information

PRAC recommendations on signals. 1.1. Loperamide – Serious cardiac events with high doses of loperamide from abuse and misuse. Accessed August 2017.

Article citation: Drug Safety Update volume 11 issue 2, September 2017: 2.

Letters sent to healthcare professionals in August 2017

In August 2017, the following letters were sent to relevant healthcare professionals to inform them of updated safety information:

- INOmax (nitric oxide) cylinders: gas delivery might stop in the month of expiry when used with the Device INOmax DSIR
- Decapeptyl SR (Triptorelin) 11.25 mg: change in salt

Article citation: Drug Safety Update volume 11 issue 2, September 2017: 3.

Medical Device Alerts issued in August 2017

In this monthly update, we highlight selected Medical Device Alerts that have been issued recently by MHRA. Please note, this is not an exhaustive list of medical device alerts. For all Medical Device Alerts from MHRA, see Alerts and recalls for drugs and medical devices.

Alerts were recently issued by MHRA about:

- Insulin pens: NovoPen Echo and NovoPen 5 (certain batches) – risk of hyperglycaemia due to cartridge holder weakening when exposed to certain household chemicals
- Antimicrobial susceptibility test: VITEK®2 Identification (ID) / Antimicrobial Susceptibility Test (AST) Cards – potential false resistance for antibiotics on the AST panel, leading to false negative ESBL test or false positive urea (URE) reaction on ID cards

Article citation: Drug Safety Update volume 11 issue 2, September 2017: 4.