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**

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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.

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This issue clarifies the type of clinical conditions and medicines that are contraindicated for use with **dabigatran,** to help minimise the known risk of haemorrhage. We also remind prescribers about the importance of monitoring renal function in patients who receive dabigatran. See article A1 for further information.

Also this month, we remind you that **solutions containing glucose** should not be used to flush arterial lines unless there is no suitable alternative, as this can cause errors in plasma glucose estimation, and has led to several cases of fatal hypoglycaemia (see article A2).

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Drug safety advice

A1 Dabigatran (Pradaxa▼): risk of serious haemorrhage – contraindications clarified and reminder to monitor renal function

Because of the risk of haemorrhage, dabigatran is contraindicated in a range of clinical conditions where the patient is at significant risk of major bleeding (listed in the main article). Dabigatran is also now contraindicated with dronedarone, and with the use of other anticoagulant agents, except when switching therapy to or from dabigatran, or with the use of unfractionated heparin for maintenance of venous or arterial catheter patency.

In addition, as exposure to dabigatran is substantially increased in patients with renal insufficiency, renal function should be assessed in all patients before starting dabigatran and at least once a year in patients older than 75 years or those with a suspected decline in renal function.

Dabigatran (Pradaxa▼) is a reversible inhibitor of free thrombin, fibrin-bound thrombin, and thrombin-induced platelet aggregation. It is licensed for primary prevention of venous thromboembolic events in adults who have had elective total hip replacement surgery or total knee replacement surgery (at 220 mg/day), and for prevention of stroke and systemic embolism in adults with non-valvular atrial fibrillation and one or more cardiovascular risk factors (at 300 mg/day).

Haemorrhage is a common adverse reaction with dabigatran. A review of world-wide data on the risk of bleeding with dabigatran, including results from clinical trials (eg, the phase III RELY study) and post-marketing surveillance, has resulted in further information and clearer advice on how best to minimise the risk of bleeding:

See: www.ncbi.nlm.nih.gov/pubmed/22700854

Updated advice on contraindications and warnings:

- Dabigatran is contraindicated in clinical conditions associated with a significant risk of bleeding, such as:
  - current or recent gastrointestinal ulceration
  - malignant neoplasms
  - recent brain or spinal injury
  - recent brain, spinal or ophthalmic surgery
  - recent intracranial haemorrhage
  - oesophageal varices
  - arteriovenous malformations
  - vascular aneurysms
  - major intraspinal or intracerebral vascular abnormalities
- The benefits and risks of starting dabigatran should also be considered carefully for patients who may have other conditions that put them at an increased risk of major bleeding (but in whom treatment with dabigatran is not contraindicated)
- Use of dabigatran is contraindicated with dronedarone, and with other anticoagulants, except when switching treatment to or from dabigatran, or with the use of unfractionated heparin for maintenance of venous or arterial catheter patency
- Concomitant use of antiplatelet agents increases the risk of major bleeding with dabigatran approximately two-fold, therefore a careful benefit-risk assessment should be made prior to initiation of treatment

Advice on switching treatment to and from dabigatran

- When switching to dabigatran, the first dose of dabigatran should be given 0-2 hours prior to the time that the next dose of the alternate medicine is due, or at the time that continuous alternate treatment is discontinued

- When switching from dabigatran to parenteral anticoagulants, an interval of 12-24 hours (dependent upon treatment indication) is recommended between treatments

- When switching from dabigatran to warfarin in patients with atrial fibrillation, the starting time of warfarin should be adjusted according to creatinine clearance (CrCL):
  CrCL ≥ 50 ml/min, start warfarin 3 days before discontinuing dabigatran
  CrCL ≥ 30 - < 50 ml/min, start warfarin 2 days before discontinuing dabigatran

  - For patients switching from warfarin to dabigatran, warfarin should be stopped and dabigatran can be given as soon as the INR is <2.0.

See product information for more details. [http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000829/human_med_000981.jsp&mid=WC0b01ac058001d124]

Reminder: importance of renal function monitoring:

- We previously advised on the importance of renal function monitoring in patients who receive dabigatran, as systemic exposure to dabigatran is substantially increased in patients with renal insufficiency (see December 2011 Drug Safety Update).

- Renal function should be assessed in all patients before starting dabigatran and at least once a year in patients older than 75 years or those with a suspected decline in renal function. Dabigatran is contraindicated in patients with severe renal impairment (creatinine clearance <30 mL/min)

December 2011 Drug Safety Update [http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON137771]

A full list of contraindications and warnings, together with updated product information for dabigatran, can be found in the individual Summaries of Product Characteristics [see the EMA website http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000829/human_med_000981.jsp&mid=WC0b01ac058001d124]

Additional advice and information for healthcare professionals:

- There is no specific antidote to dabigatran and excessive anticoagulation may require interruption of treatment

- In the event of haemorrhagic complications, dabigatran must be discontinued and the source of the bleeding investigated. Adequate diuresis must be maintained, and surgical haemostasis and blood volume replacement should be undertaken at the clinicians's discretion

- Additional measures may be considered in the treatment of serious haemorrhage, including: activated prothrombin complex concentrates, recombinant factor VIIa, or concentrates of coagulation factors II, IX and X, and platelet concentrates where appropriate. Coagulation tests may become unreliable following administration of reversing agents and measurements may remain elevated despite administration. Caution must be exercised when interpreting these results.

Further information:

Information on dabigatran from the European Medicines Agency [http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000829/human_med_000981.jsp&mid=WC0b01ac058001d124] and http://www.ema.europa.eu/docs/en_GB/document_library/Summary_of_opinion/human/000829/WC500130142.pdf]

BNF section 2.8.2 Oral anticoagulants [www.medicinescomplete.com/mc/bnf/current/2791.htm]

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A2 Glucose solutions: false blood glucose readings when used to flush arterial lines, leading to incorrect insulin administration and potentially fatal hypoglycaemia

There have been reports of glucose-containing solutions being inadvertently used to flush arterial lines of patients in intensive care units. As a result blood samples drawn from the lines gave falsely high plasma glucose readings resulting in inappropriate insulin administration. These actions lead to several cases of hypoglycaemia, some of which were fatal.

Clinicians are reminded that solutions containing glucose should not be used to flush arterial lines, unless there is no suitable alternative. Saline infusions are recommended as the flush solution for arterial lines, to minimise the risk of contamination and adverse effects.

If samples are drawn from arterial lines for estimation of biochemistry, a minimum volume of three times the dead space of the cannula system should be discarded first to avoid contamination.

Arterial lines are routinely fitted for severely ill patients in critical care and are flushed with a solution to maintain patency, and ensure that blood does not clot in the line. Saline is recommended as the flush solution for arterial lines.

Case reports of fatal hypoglycaemia

There are several examples of glucose solutions being inadvertently and incorrectly used to flush arterial lines[1,2,3]. This has lead to inaccuracies in blood glucose measurements, which resulted in unnecessary administration of insulin and subsequent cases of hypoglycaemia, some of which have been fatal.

It is important to note that even a fraction of a millilitre of glucose-containing solution is likely to raise the measured plasma glucose to extremely high levels (5% glucose infusate has approximately 280 mmol/L of glucose).

Care should be taken when selecting the flush solution for arterial lines – saline infusions are recommended.

Advice for healthcare professionals:

- Do not use glucose-containing solutions as infusates for maintaining arterial line patency, unless there are no suitable alternatives.
- Saline infusions are recommended as the flush solution for arterial lines, to minimise the risk of incorrect blood glucose estimation and inappropriate insulin administration
- If samples are drawn from arterial lines for estimation of biochemistry, a minimum volume of three times the dead space of the cannula system should be discarded first to avoid contamination[4]
- Remain vigilant when selecting a solution for arterial line infusate. Similarities between glucose and saline solution bags means that confusion may occur
- Ensure that the arterial infusion line length is kept to the minimum necessary

References:

1. Sinha S, Jayaram R, Hargreaves CG. *Anaesthesia* 2007; **62**(6): 615-620

2. Panchagnula U, Thomas AN. *Anaesthesia* 2007; **62**(10):1077-1078

3. National Patient Safety Agency, 2008. New guidance issued following problems with infusions and sampling from arterial lines [http://www.npsa.nhs.uk/corporate/news/new-guidance-issued-following-problems-with-infusions-and-sampling-from-arterial-lines/?locale=en]

4. Burnett RW, Covington AK, Fogh-Andersen N, et al. *Eur J Clin Chem Clin Biochem* 1995; **33**(4): 247-253

Article citation: Drug Safety Update July 2011 vol 5, issue 12: A2.