IRISH MEDICINES BOARD

Drug Safety NEWSLETTER

35th EDITION

Bisphosphonates and Osteonecrosis of the Jaw: Update on Risk Minimisation including New Recommendations on Preventative Dental Measures

Bisphosphonates are a class of medicines approved for various indications related to their inhibitory effect on bone resorption in certain malignant and benign diseases, including prophylaxis and treatment of osteoporosis; treatment of Paget's disease; and as part of some cancer regimens, particularly for metastatic bone cancer and multiple myeloma.

The risk of osteonecrosis of the jaw (ONJ) in association with the use of bisphosphonates has been closely monitored and reviewed at EU level on several occasions, with a number of risk minimisation measures taken, including updates to the product information and communication to healthcare professionals. The most recent review of information on the risk of bisphosphonate associated ONJ included assessment of the currently available published literature and data provided by the Marketing Authorisation Holders (including data from experimental and preclinical studies, clinical trials, and post-marketing reports), together with current guidelines produced by learned societies. The review also incorporated advice from a group of experts representing all areas of medicine where bisphosphonates are used, dentistry and bone surgery, and representatives of patients' organisations.
The European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) reached conclusions on the currently available evidence on four main areas: definition and diagnosis of ONJ related to bisphosphonates; possible underlying pathophysiological mechanism(s); risk stratification; and risk minimisation.

Whilst it is recognised that risk factors for ONJ are multiple and currently not fully elucidated, the most significant risk factors for the development of ONJ in association with bisphosphonates are considered to be bisphosphonate potency, route of administration and cumulative dose of bisphosphonate exposure. A history of dental disease, including invasive dental procedures, dental trauma, periodontal disease, and poorly fitting dentures is also associated with an increased risk of ONJ.

Further research is needed to increase knowledge about the underlying mechanisms and risk factors for ONJ, and about how best to minimise these risks. The EU regulatory authorities will explore strategies to promote this research and the CHMP has adopted a definition of ONJ related to bisphosphonates to facilitate future case reporting and research. However, healthcare professionals should consider these risk factors when evaluating an individual's risk of developing ONJ.

In this edition

- Bisphosphonates and Osteonecrosis of the Jaw: Update on Risk Minimisation including New Recommendations on Preventative Dental Measures
- HMG-CoA reductase inhibitors and risk of sleep disturbances, memory loss, sexual dysfunction, depression and interstitial lung disease
- Antipsychotics and Risk of Venous Thromboembolism
- Ceftriaxone – Contraindication in newborns and risk of calcium-ceftriaxone precipitation when administered/mixed with solutions containing calcium.

Advice for Healthcare Professionals

- The risk of developing ONJ in association with oral bisphosphonates seems to be low. The risk of ONJ is substantially greater for patients receiving intravenous bisphosphonates for cancer indications than for patients receiving oral bisphosphonates for osteoporosis or Paget's disease.

- There is clear evidence to suggest bisphosphonate-specific and indication-specific risk factors for the devel- opment of ONJ such as potency (highest for zoledronic acid), route of administration (e.g. intravenous ibandronic acid, pamidronic acid and zoledronic acid); and cumulative dose. The evidence base is less robust for other proposed risk factors (e.g. duration and type of malignant disease, concomitant treatment, smoking, and comorbid conditions). However, healthcare professionals should consider these risk factors when evaluating an individual's risk of developing ONJ.

- A history of dental disease – including invasive dental procedures, dental trauma, periodontal disease, and poorly fitting dentures – is associated with an increased risk of ONJ.

Risk Minimisation – Recommendations for preventative dental measures (Baseline assessment and ongoing monitoring)

For patients receiving bisphosphonates for CANCER indications; the recommendations are as follows:

Before starting treatment with bisphosphonates:

- An oral and dental assessment should be performed by a dentist or oral surgeon to optimise dental health. If dental treatment is required, this should take place as quickly as possible before start of bisphosphonate treatment. If urgent treatment with a bisphosphonate is necessary, this should not be delayed and the patient should be referred in an expedited manner for a dental examination.

During treatment with bisphosphonates:

- Patients should be advised of the importance of maintaining good oral hygiene in preventing dental disease.
- There is a need to ensure oral and dental follow-up performed by a dentist.
- Dental examination is recommended as soon as the patient develops oral symptoms, such as pain or swelling.
- Dental interventions should be as conservative and preservative as possible (preservation of tooth).

For patients receiving bisphosphonates for NON-CANCER indications, the recommendations are as follows:

Before starting treatment with bisphosphonates:

- A dental examination should be performed if the dental status of the patient is poor. Since the start of bisphosphonate treatment may not be urgent in this setting, oral and dental assessment may be followed by dental care if necessary.

During treatment with bisphosphonates:

- Patients should be advised of the importance of maintaining good oral hygiene to prevent dental disease.
- Routine dental checkups by a regular dentist are recommended. Dental examination is recommended as soon as the patient develops dental problems whilst on treatment. Dental interventions should be as conservative and preservative as possible.

Key message: All patients with cancer should have a dental check-up before bisphosphonate treatment. All other patients who start bisphosphonates should have a dental examination if they have poor dental status. During bisphosphonate treatment, patients should be advised to maintain good oral hygiene, receive routine dental check-ups, and report any oral symptoms such as dental mobility, pain or swelling.

HMG-CoA reductase inhibitors and risk of sleep disturbances, memory loss, sexual dysfunction, depression and interstitial lung disease

An EU review of the class of HMG-CoA reductase inhibitors (atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin and simvastatin) was triggered by spontaneously reported cases and publications in the medical literature suggesting potential associations between statins and sleep disturbances, memory loss, sexual dysfunction, depression, interstitial lung disease and micturition disorders. The conclusion of this review has resulted in EU recommendations to update and harmonise the product information for statins across the EU to include reference to such effects as possible adverse reactions and to provide advice to stop treatment with statins, should a patient develop interstitial lung disease.

The review considered data from spontaneous reports, clinical trials and the medical literature. Data from clinical trials provided evidence that for some statins the rates of sleep disturbances and memory loss were higher in the active than in the placebo group. In addition, spontaneous case reports included some cases with a temporal relationship, experience of positive dechallenge and positive rechallenge, providing further supportive evidence of a possible causal relationship of sleep disturbances (e.g. sleeplessness, nightmares) and memory loss. The spontaneous case reports also provided evidence that statins may be associated with sexual dysfunction, depression and interstitial lung disease. The available evidence did not suggest that micturition disorders were associated with statins. It is recognised that the amount of evidence for the different adverse reactions varied among the statins but considered that there was no robust evidence to discriminate between the individual statins in terms of their risks.

Risk Minimisation

Key Message: Stop statin if a patient develops interstitial lung disease. Statins may cause sleep disturbances, memory loss, sexual dysfunction, depression and interstitial lung disease.

Antipsychotics and Risk of Venous Thromboembolism

The Pharmacovigilance Working Party (PhVWP) of the European Medicines Agency recently completed a European review of the risk of Venous thromboembolism (VTE) in association with the use of antipsychotics. The review was based on data from spontaneous adverse reaction reports and published literature. The limitations of both information sources, such as the lack of randomised controlled trial data, the heterogeneity of published studies and potential confounding factors such as sedation and weight gain, commonly present in antipsychotic users were considered in the assessment, which concluded that an association between VTE and antipsychotics cannot be excluded. Distinguishing different risk levels between the various active substances was not possible.

As a result of this review, it was recommended that the product information should be updated to indicate that cases of VTE (including pulmonary embolism and deep vein thrombosis) have been reported with antipsychotic medicines, highlighting the importance of identifying risk factors for VTE before and during treatment and taking appropriate preventive measures. Implementation of these recommendations is underway for relevant products authorised for use in Ireland.

Risk Minimisation

Key Message: Identify risk factors for VTE for preventive action before and during treatment with antipsychotics.

Call for reporting

Please remember that you can report **suspected** adverse reactions to medicines to the IMB, either on-line on the IMB website at www.imb.ie or using a downloadable version of the adverse reaction report form also available from the IMB's website.

Ceftriaxone - Contraindication in newborns and risk of calcium-ceftriaxone precipitation when administered/mixed with solutions containing calcium.

Ceftriaxone (Rocephin) is a broad-spectrum antibiotic that is used to treat infections known or likely to be due to one or more susceptible micro-organisms and when parenteral therapy is needed. Ceftriaxone can be given by deep intramuscular injection, slow intravenous injection, or by slow intravenous infusion after reconstitution of the solution. A review of the risk of precipitation of ceftriaxone and calcium with intravenous co-administration was recently concluded by the Pharmacovigilance Working Party (PhVWP) of the European Medicines Agency.

A number of serious, and in some cases, fatal reactions in premature babies or neonates treated concomitantly with intravenous ceftriaxone and calcium gluconate have been reported. Some of these reactions were due to the formation of a crystalline precipitate in the tubing and/or the pulmonary or renal parenchyma. In at least one case, ceftriaxone and calcium were given at different times and through different intravenous lines. Data from in vitro studies demonstrated that neonates may have an increased risk of precipitation of ceftriaxone-calcium compared to other age groups due to their lower blood volume and longer elimination half-life of ceftriaxone compared with adults. The available data do not contain reports of confirmed intravascular precipitates in patients other than neonates.

As a result, the warnings and precautions for use of ceftriaxone with solutions containing calcium have been strengthened, to avoid any risk of physicochemical incompatibility. It is recommended that in patients of any age, ceftriaxone must not be mixed or administered simultaneously IV with any calcium-containing solution, even via different infusion lines or at different infusion sites. However, in patients older than 28 days sequential administration may be feasible when following certain preventive measures. Likewise, preventative measures are considered necessary in patients requiring continuous total parenteral nutrition (TPN).

Advice for Healthcare Professionals

- Intravenous ceftriaxone administration is contraindicated in premature neonates up to a corrected age of 41 weeks (week of gestation + weeks of life), and in neonates with jaundice, or who are hypoalbuminaemic or acidotic because these are conditions in which bilirubin binding is likely to be impaired.
- Ceftriaxone is contraindicated in neonates (up to 28 days of age) if they require (or are expected to require) IV calcium treatment.
- In patients of any age, ceftriaxone must not be mixed or administered simultaneously with any calcium-containing IV solutions, even via different infusion lines or at different infusion sites.
- In patients older than 28 days of age, ceftriaxone and calcium-containing solutions may be administered sequentially, if infusion lines at different sites are used, or if the infusion lines are replaced or thoroughly flushed between infusions with physiological salt-solution to avoid precipitation.
- In patients requiring continuous infusion with calcium-containing TPN solutions, healthcare professionals may wish to consider the use of alternative antibacterial treatments which do not carry a similar risk of precipitation. If use of ceftriaxone is considered necessary in patients requiring continuous nutrition, TPN solutions and ceftriaxone can be administered simultaneously, albeit via different infusion lines at different sites. Alternatively, infusion of TPN solution could be stopped for the period of ceftriaxone infusion, considering the advice to flush infusion lines between solutions.

Risk Minimisation:

Key message: Ceftriaxone and calcium-containing solutions contraindicated in neonates in certain conditions and should not be mixed or administered simultaneously for intravenous use in patients of any age.