boletim de FARMACOVIGILÂNCIA

REPÚBLICA PORTUGUESA
SAÚDE

Infarmed
Autoridade Nacional do Medicamento e Produtos de Saúde, I.P.

VOLUME 20
NUMBER 3
SEPTEMBER 2016

From the Editor

*Starting from this issue the Portuguese pharmacovigilance bulletin will begin to be published monthly. The Boletim's health professional readership will be receiving safety information even more on the dot every month at the INFARMED website where the publication's pdf file can be accessed and downloaded. You can also choose to get a link to each new issue in your mailbox – all you have to do is click **here** and subscribe for free.*

Agomelatine
Urinary retention

Quick Read
The melatoninergic agonist and 5-HT2c antagonist agomelatine, similarly to other antidepressant agents, may in rare cases be associated with the occurrence of urinary retention.

Agomelatine is a melatoninergic (MT1 and MT2 receptor) agonist and a 5-HT2c antagonist used in the treatment of episodes of major depression in adult patients. It increases the release of noradrenaline and dopamine from the frontal cortex while having no effect on the extracellular levels of serotonin.

During its routine pharmacovigilance activities and based on six cases from the European adverse drug reaction database EudraVigilance, the European Medicines Agency (EMA) recently raised a safety signal to do with agomelatine and urinary retention, an adverse effect previously known to rarely occur with other antidepressants.

Taking into account the available data and the concluded assessment, a causality relationship seems to be possible. Its precise mechanism remains to be clarified, although it is known that agomelatine can promote the stimulation of adrenal receptors in the lower urinary tract.

In September 2016, EMA recommended that the marketing authorization (MA) holders of medicinal products containing agomelatine submit the following changes to the SmPC (Summary of the Product's Characteristics):

Section 4.8. Undesirable effects
Renal and urinary disorders
(Frequency) rare: Urinary retention

Leonor Chambel

INDEX CARD

Diretor: Fátima Canedo
Editor: Rui Pombal
Assistant Editor: Leonor Nogueira Guerra
Contributors: Ana Sofia Martins, António Leandro Ponte, Cristina Mousinho, Fátima Bragança, Fátima Hergy, Leonor Chambel, Leonor Nogueira Guerra, Magda Pedro, Márcia Silva, Margarida Guimarães, Pedro Marques Silva, Sílvia Duarte
Publishing Assistant: Inocência Pinto
Advisory Board: Conselho Diretivo do INFARMED, I.P. – Comissão de Avaliação de Medicamentos
INFARMED – Autoridade Nacional do Medicamento e Produtos de Saúde, I.P.
Parque de Saúde de Lisboa, Av. do Brasil, N.º 53, 1749-004 Lisboa
Phone: +351 217 987 100
E-mail: infarmed@infarmed.pt
Design and production:: Letras & Sinais, Comunicação e Imagem, Lda.
ISSN: 0873-7118

Alerts and News at the Infarmed website
on Linkedin
and Twitter

For news and publications, just use thirty seconds of your time and register here!

Warfarin
Risk of calciphylaxis

Quick Read

Calciphylaxis is a rare, high-mortality syndrome of vascular calcification and skin necrosis whose pathophysiology still is to a large extent unknown. It can be associated with various conditions including renal failure. Rare cases of calciphylaxis have been described in patients being treated with warfarin, even in the absence of kidney disease.

Warfarin is a vitamin K antagonist used as an oral anticoagulant in the treatment and prophylaxis of thromboembolic diseases. The pathophysiology of calciphylaxis is still relatively obscure and it is probably the result of multiple comorbidity factors.

During its routine pharmacovigilance activities and based on cases from the literature[1 - 18], Sweden raised a safety signal concerning calciphylaxis and the use of warfarin. Overall those articles included a total of twenty cases of warfarin-induced calciphylaxis.

Taking into account the available data, the European Medicines Agency (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) agreed to request from the marketing authorization (MA) holders a cumulative review of all calciphylaxis and related cases. It was concluded that there was a causal relationship and the following changes to the SmPC (Summary of the Product's Characteristics) were recommended:

Section 4.4 – Special warnings and precautions for use

Calciphylaxis is a rare syndrome of vascular calcification with cutaneous necrosis, associated with high mortality. The condition is mainly observed in patients with end-stage renal disease on dialysis or in patients with known risk factors such as protein C or S deficiency, hyperphosphataemia, hypercalcaemia or hypoalbuminaemia. Rare cases of calciphylaxis have been reported in patients taking warfarin, also in the absence of renal disease. In case calciphylaxis is diagnosed, appropriate treatment should be started and consideration should be given to stopping treatment with warfarin.

Section 4.8 – Undesirable effects
Skin and subcutaneous disorders
Frequency Not known: calcyphilaxis

Leonor Chambel

REFERENCES:

[1] *Savoia F et al. Calciphylaxis in dialysis patients, a severe disease poorly responding to therapies: Report of 4 cases. Minerva Dermatologica 148: 531-536, No. 5, Oct 2013.*
[2] *Breakey W et al. Warfarin-induced skin necrosis progressing to calciphylaxis. Journal of Plastic, Reconstructive and Aesthetic Surgery: JPRAS 67: e244-e246, No. 10, Oct 2014.*
[3] *Gallimore GG et al. Curious case of calciphylaxis leading to acute mitral regurgitation. BMJ Case Reports: 30 Apr 2014.*
[4] *Crotty R et al. Heparin, warfarin, or calciphylaxis?. American Journal of Hematology 89: 785-6, No. 7, Jul 2014.*
[5] *Madsen N et al.. Wafarin induced calciphylaxis. The Journal of Rheumatology 41: 1549 abstr. 208, No. 7, 1 Jul 2014.*
[6] *Lee C et al.. Warfarin-associated calciphylaxis in a patient with normal renal function. Vascular Medicine 19: 329-330, No. 4, Aug 2014.*
[7] *Kwong AJ et al. Calciphylaxis in patient without renal failure. Journal of General Internal Medicine 29 (Suppl.):S327, No. 1, Apr 2014.*
[8] *Spanakisw EK et al. Nonuremic calciphylaxis precipitated by teriparatide [rhPTH(1-34)] therapy in the setting of chronic warfarin and glucocorticoid treatment. Osteoporosis International 25: 1411-1411, No. 4, Apr 2014.*
[9] *Thet Z et al. A case report of calciphylaxis: Sequential calciphylaxis and warfarin induced skin necrosis. Nephrology 18 (Suppl. S1): 75 abstr. 240, Sep 2013.*
[10] *Saifan C et al. Warfarin-induced calciphylaxis: A case report and review of literature. International Journal of General Medicine 6: 665-669, 9 Aug 2013.*
[11] *Hafiji J et al. Warfarin-induced calciphylaxis successfully treated with sodium thiosulphate. Australasian Journal of dermatology 54: 133-135, No. 2, May 2013.*
[12] *Baldwin C et al. Multi-intervention management of calciphylaxis: A report of 7 cases. American Journal of Kidney Diseases 58: 988-991, No. 6, Dec 2011.*
[13] *Cadavid JC et al.. Warfarin-induced pulmonary metastatic calcification and calciphylaxis in a patient with end-stage renal disease. Chest 139: 1503-1506, No. 6, Jun 2011.*
[14] *Banerjee C et al.. Atypical calciphylaxis in a patient receiving warfarin then resolving with cessation of warfarin and application of hyperbaric oxygen therapy. Clinical and Applied Thrombosis/ Hemostasis 16: 345-350, No. 3, Jun 2010.*
[15] *Swanson AM et al.. Calciphylaxis associated with chronic inflammatory conditions, immunosuppression therapy, and normal renal function: a report of 2 cases. Archives of Dermatology 145: 723-725, No. 6, Jun 2009.*
[16] *Asobie N et al.. Calciphylaxis in a diabetic patient provoked by warfarin therapy. CIlinical and Experimental Dermatology 33: 324-344, No. 3, May 2007.*
[17] *Almafragi A et al.. Calciphylaxis in a cardiac patient without renal disease. Acta Cardiologica 64: 91-93, No. 1, feb 2009.*
[18] *Huang Y-C et al.. Warfarin-induced calciphylaxis in a chronic hypercalcemic patient. Indian Journal of Dermatology, venereology and Leprology 79: 135: No. 1, Jan-Feb 2013.*

Recombinant factor VIII
Risk of development of inhibitor antibodies

Quick Read
The risk of developing inhibitors in patients with severe haemophilia A does not seem to be significantly different across the various products containing recombinant factor VIII.

The development of factor VIII alloantibodies is associated with a reduction of haemostatic effect and is the most serious and challenging complication of haemophilia A treatment. It usually occurs during the initial exposure to factor VIII, that is, in small children.

A metaanalysis has been concluded which assessed the risk of development of antibodies against recombinant factor VIII in previously untreated patients with severe haemophilia A (factor VIII levels <1%). Medicines included in this metaanalysis were the centralized products containing octocog alfa (Advate, Helixate Nexgen, and Kogenate Bayer) and moroctocog alfa (Refacto and Refacto AF), as well as other recombinant anti-haemophilia factors authorized at national level.[1-3]

The European Medicines Agency (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) highlighted some limitations in that analysis including the possibility of residual confounding. It was concluded that an increased risk of inhibitor development in previously untreated patients with severe haemophilia A was not confirmed for either Kogenate Bayer or Helixate NexGen, when compared with other recombinant factor VIII products. These conclusions are in agreement with a previous ***2013 review***.

Márcia Silva

REFERENCES:
[1] *Gouw SC et al. PedNet and RODIN Study Group. Factor VIII products and inhibitor development in severe hemophilia A. N Engl J Med 2013; 368: 231-9.*
[2] *Collins PW et al. Factor VIII brand and the incidence of factor VIII inhibitors in previously untreated UK children with severe haemophilia A, 2000-2011. Blood. 2014; 124(23): 3389-97.*
[3] *Calvez T et al. Recombinant factor VIII products and inhibitor development in previously untreated boys with severe hemophilia A. Blood. 2014; 124(23): 3398-408*

ADRs in the Literature

Single exposure to general anaesthesia in early childhood does not seem to be associated with untoward neurocognitive outcomes until as late as adolescence.

In this interesting and original study, the authors tried to find out whether a single exposure to anaesthetics in otherwise healthy children could be associated with neurocognitive development or abnormal behaviour disorders later in childhood.

They studied a cohort of pairs of siblings not older than 36 months of which one had been submitted to general anaesthesia for inguinal hernia repair (mean age at time of surgery: 17.3 months). At the moment the study was undertaken the subjects were between 8 and 15 years of age and the "global cognitive function" outcome was assessed prospectively with retrospective data since anaesthetic exposure.

No significant differences were found within the pairs of siblings in their IQ scores, namely in terms of memory/learning, motor/processing speed, visuospatial function, attention, executive function, language, behaviour. Future studies could look into repeat or prolonged exposures and subgroups of special vulnerability

Sun LS et al. JAMA. 2016;315(21):2312-2320

Educational Materials published on the Infarmed website

Medicinal product (DCI)	Click on the links (in Portuguese)
Eliquis (apixaban)	***Information for physicians*** Guia do prescritor – 4.ª versão Published on 10-08-2016
Exelon/Prometax (rivastigmine)	***Information for patients*** Cartão de memória para o doente – 3.ª versão Published on 19-07-2016
Keytruda (pembrolizumab)	***Information for physicians*** Brochura de informação para profissionais de saúde – 2.ª versão ***Information for patients*** Brochura de informação para o doente – 2.ª versão Cartão de alerta para o doente – 2.ª versão Published on 01-07-2016
Opdivo (nivolumab	***Information for physicians*** Guia de controlo de reações adversas imunitárias para o médico 3.ª versão ***Information for patients*** Cartão de alerta do doente – 3.ª versão Published on 19-08-2016
Pamidronato Hikma (sodium pamidronate)	***Information for patients*** Cartão de alerta para o doente – 1.ª versão Published on 04-07-2016
Pradaxa (dabigatran)	***Information for physicians*** Guia de prescrição (FANV, TVP e EP) (indicações cardiovasculares) 9.ª versão Guia de prescrição para a prevenção primária de fenómenos tromboembólicos venosos – 9.ª versão Publicados a 06-07-2016
Rivastigmina Mylan (rivastigmine)	***Information for patients*** Cartão de memória para o doente – 1.ª versão Published on 06-07-2016
Tarceva (erlotinib)	***Information for healthcare professionals*** Material educacional para profissionais de saúde sobre recomendações de dose e abordagem da doença pulmonar intersticial (DPI) – 3.ª versão Published on 19-08-2016

Compiled by Magda Pedro

Communications to healthcare professionals

Medicinal product (DCI)	Click on topic for details (in Portuguese)
Adempas (riociguat)	New contraindication in patients with pulmonary hypertension associated with idiopatic interstitial pneumonia Published on 05-07-2016
Zydelig (idelalisib)	Recommendation update (indicatons, PJP prophylaxis, periodic clinical and laboratory monitoring) Published on 22-08-2016

Compiled by Ana Sofia Martins