Prémio Desenvolvimento Sustentável 2010/11
Ministério da Saúde

boletim de FARMACOVIGILÂNCIA

VOLUME 15
NUMBER 3
3RD QUARTER 2011

infarmed
Autoridade Nacional do Medicamento e Produtos de Saúde I.P.

From the Editor

In this issue of the Boletim, our attention is brought to the paradox of atypical fractures occurring under anti-osteoporotic therapy, namely with biphosphonates. Not rarely, only the continuing use of medicines in populations throughout a certain length of time allows for evidence to surface for adverse effects that may not have been detected as such until then. Pharmacovigilance makes it possible for the safety profile of medicinal products to be updated on an ongoing basis, as experience and research generate novel data. Active participation on the part of health professionals is of crucial importance. In fact, critical data may be produced by their reports of suspected adverse reactions which are considered unusual or in any other way unexpected.

Biphosphonates
Risk of atypical femoral fractures

EMA has reviewed the information for biphosphonates. These are medicines used in the treatment and prevention of bone disorders, including hypercalcaemia, as well as for the prevention of bone problems in cancer patients, and for the treatment of osteoporosis and Paget's disease. The class of biphosphonates includes alendronic acid, chlodronic acid, etidronic acid, ibandronic acid, neridronic acid, pamidronic acid, risedronic acid, and tiludronic acid.

The following are key messages from the above review:

• Atypical femoral fractures associated with treatment with biphosphonates have been reported at **very low frequency**, mainly in patients receiving **long-term therapy** for osteoporosis.

• These fractures are often **bilateral**. The contralateral femur should therefore be examined in patients on biphosphonates who have sustained a fracture of the femoral axis. Depending on the individual benefit/risk assessment, discontinuing therapy with biphosphonates in the presence of an atypical femoral fracture should be considered whilst the patient's full assessment is ongoing.

• Atypical femoral fractures can occur **following minimal or no trauma**. Some patients report **hip, thigh or groin pain**, often associated with x-ray features of stress fracture weeks or months before they present with a complete femoral fracture. These fractures are reportedly difficult to heal. Any patient presenting with the above algic complaints should be examined for a potential incomplete femoral fracture.

• Atypical femoral fractures are considered to be a **class effect of biphosphonates** and, as such, a warning on this type of risk is going to be added for all medicines containing biphosphonates.

• The **benefit/risk ratio** of biphosphonates in their authorized indications remains **positive**.

• Optimal duration of biphosphonate treatment for osteoporosis has not been established. The need for such therapy should be periodically re-evaluated by applying the benefit/risk ratio concept to each individual patient, especially **after 5 or more years** of use.

For further information, the European Commission Decision can be accessed at:

http://www.infarmed.pt/pt/medicamentos/uso_humano/arbitragens/concluidas.html
http://ec.europa.eu/index_en.htm.

NB: *The CHMP has adopted the ASBMR (American Society for Bone and Mineral Research) definition of atypical femoral fracture: Shane et al. Atypical subtrochanteric and diaphyseal femoral fractures: report of a task force of the American Society for Bone and Mineral Research. J Bone Miner Res 2010; 25: 2267-2294.*

Margarida Guimarães

What do they stand for?!

ADR Adverse Drug Reaction
CHMP Committee for Medicinal Products for Human Use
EMA European Medicines Agency
PIL Patient Information Leaflet
MA Marketing Authorisation
SPC Summary of the Product's Characteristics

How can I report an adverse reaction?

Postage Paid Card

Also online at:
www.infarmed.pt/pt/vigilancia/medicamentos/reacções_adversas/fichas_notificação/index.html

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Nimesulide
Not for painful osteoarthritis

EMA has concluded that the benefits of medicines containing nimesulide are still higher than the attendant risks in what concerns **patients with acute pain or with primary dysmenorrhoea**. However, these medicines should **not** be used for the symptomatic treatment of painful **osteoarthritis**.

EMA has considered that the use of nimesulide in the symptomatic treatment of painful osteoarthritis increases the probability that it may be used for long periods of time, consequently increasing the risk of liver dysfunction.

Nimesulide should therefore not be prescribed for the treatment of painful osteoarthritis, rather only as second line therapy for acute pain and dysmenorrhoea.

Vareniclin
Benefit/risk ratio still positive

The CHMP at EMA and the European Pharmacovigilance Working Party (PhVWP) have concluded that the benefits of Champix® (vareniclin) for smoking cessation outweigh the **slightly increased risk of cardiovascular events** reported by the authors of an article recently published in the Canadian Medical Association Journal.

The study analysed the number of cardiovascular events which occurred in a total of 8,216 subjects who were taking either Champix® or placebo, from a total of fourteen randomised clinical trials with a duration of approximately one year. Those events included heart attack, infarction, heart rhythm disturbance, cardiac failure, and death related to cardiovascular problems. Most studies included over 700 patients with preexisting cardiovascular disease.

The CHMP has requested that the MA Holder include further information on cardiovascular effects in the SPC and Information Leaflet. This safety data update is expected to be finalised very soon.

Patients currently under treatment with Champix® should not stop taking this medicine without first discussing the matter with their doctor at their next appointment.

Pioglitazone
Risk of bladder cancer slightly increased

EMA has recently finalised a review on the risk/benefit balance of medicinal products containing pioglitazone. It has concluded that there is a **slightly increased risk of bladder cancer** in diabetic patients, but these products are still a valid therapeutic option for some type 2 diabetics.

Pioglitazone's benefits still outweigh its risk in patients who respond to the treatment adequately. However, taking into account the above data, EMA and Infarmed recommend that measures to reduce the risk of bladder cancer be taken, namely:

- Pioglitazone should not be prescribed to patients who have, or have had, bladder cancer, or who present with gross haematuria of unknown origin.

- Before starting treatment with pioglitazone, risk factors for bladder cancer should be sought (age, smoking, exposure to certain chemical or medicinal products).

- In older patients, treatment with pioglitazone should be started at the lowest dose, since these patients are at increased risk of bladder cancer and cardiac failure.

- Pioglitazone therapy should be reviewed every three to six months. Treatment should be discontinued whenever the attendant benefit is not of sufficient magnitude.

Dexrazoxan
restrictions to use

Dexrazoxan is indicated in cancer patients for the prevention of long-term cardiac toxicity caused by treatment with doxorubicin and epirubicin. A safety data review on dexrazoxan has been prompted by a suspected increased risk of occurrence of **acute myeloid leukaemia** (AML) and **myelodysplastic syndrome** (MDS).

EMA recommends restricting the use of dexrazoxan to adult patients with **metastatised or advanced stage breast cancer**, who have received a cumulative dose equal to or higher than 300 mg/m^2 of doxorubicin or 540 mg/m^2 of epirubicin (antineoplastic anthracyclines). The CHMP has also recommended that these medicinal products be **contraindicated** in **children and adolescents** up to 18 years of age.

When prescribing dezrazoxan, physicians should bear in mind the above new restrictions, as well as carefully ponder the balance between the cardioprotective effects and the short and long-term risks, especially AML and MDS.

Dronedarone (Multaq®)
Cardiovascular, hepatic and pulmonary risks

Multaq® is an antiarrhythmic agent indicated in adult patients with non-sustained atrial fibrillation. It is not marketed in Portugal.

EMA has finished a benefit/risk review of Multaq® which had been prompted by the occurrence of cases of serious liver impairment in patients treated with this medicine. During the review, the CHMP was informed that the PALLAS clinical trial had been stopped on account of serious cardiovascular adverse effects. Based on the available data, the CHMP has concluded that Multaq® increases the **risk of liver and pulmonary impairment** when used according to the data contained in the SPC. Although the analysis of data from the PALLAS study does show **increased risk for cardiovascular adverse reactions in some patients** with non-sustained atrial fibrillation, Multaq® still is a valid therapeutic option, provided risk minimisation measures are taken:

- Treatment should be limited to patients with paroxysmal or persistent atrial fibrillation, as soon as sinus rhythm has been resumed, not while the patient is still having atrial fibrillation.
- Treatment should only be started by a specialist and after the therapeutic alternatives have been considered. Use of this medicine should be monitored.
- It should not be used in patients with sustained atrial fibrillation, cardiac failure, or left ventricular dysfunction.
- If atrial fibrillation recurs, consideration should be given to discontinuing the treatment.
- This medicine should not be used in patients who have had liver or pulmonary impairment resulting from treatment with amiodarone or any other antiarrhythmic agent.
- Liver, pulmonary and cardiac function should be regularly monitored. Special attention should be given to liver function within the first few weeks of treatment.

Orlistat
How significant is liver risk?

EMA has started a safety data review concerning medicinal products containing orlistat (in Portugal marketed as Xenical® and Alli®) [manter ® em superscript], aiming to evaluate the impact of reported **rare cases** of liver impairment on the benefit/risk ratio and on the conditions of use of these medicines indicated in the treatment of obesity in association with diet.

The risk of adverse liver reactions with orlistat is well known and has been monitored by EMA since MA was first given.

Overall, with orlistat 120 mg, between 1997 and January 2011, 21 cases of suspected serious liver toxicity were reported for which a causality nexus could neither be excluded nor confirmed. The number of reports should take into account the cumulative use of these medicinal products in a universe of 38 million patients.

From May 2007 until January 2011 a total of 9 suspected cases of serious liver injury were reported for orlistat 60 mg. In some of these cases there were also other possible explanations for hepatic dysfunction, and in others still the data available were not sufficient for a conclusive assessment. These nine cases should also be seen against a background of cumulative use by a universe of 11 million patients.

Anti-Influenza A (H1N1) Vaccine
Use limitations for individuals younger than 20

Following a review on Pandemrix® and narcolepsia, EMA has recommended that this vaccine should only be used in subjects aged less than 20 years in case the seasonal flu vaccine is not available and immunisation againts influenza A (H_1N_1) is still necessary; for example, in people at risk of complications from influenza. On the other hand, EMA has confirmed that the vaccine's benefit/risk ratio remains positive for subjects older than 20 years.

EMA and Infarmed recommend the following to doctors and patients:

- Pandemrix® should only be used in patients younger than 20 **in case** the seasonal flu vaccine is not available **and** immunisation against influenza A (H_1N_1) is still necessary.
- People vaccinated with Pandemrix® who have no symptoms of narcolepsy do not need any additional precautions.
- Anynone (whether vaccinated or not) who presents with symptoms that are suggestive of narcolepsy, such as inexplicable daytime sleepiness, should see their doctor or seek advice from their pharmacist.

Adverse effects with pandemic flu vaccine in health professionals

The vaccination campaign against pandemic influenza A (H_1N_1) in Portugal was started on 26th October 2009, initially with Pandemrix® which had been authorised on 29th September. Priority groups for vaccination were then defined aiming to protect the more vulnerable segments of the population, to reduce morbidity and mortality, to keep essential services operating, and to limit the rapid spread of the infection. Health professionals were included in those priority groups.

The Northern Portugal Pharmacovigilance Unit (UFN) carried out a study whose objective was to identify post-immunisation adverse effects (AEs) with Pandemrix® in health professionals. This particular population was chosen in that health professionals have specifically relevant knowledge and are able to report adverse reactions, and therefore able to produce valuable information as regards the full picture of the safety profile of the vaccine at hand.

A post-vaccination adverse reaction report questionnaire was designed and handed out to health professionals vaccinated between 26th October 2009 and 31st January 2010 and who were working in three major hospital units in the North of Portugal – São João Hospital, Pedro Hispano Hospital, and Centro Hospitalar do Porto.

All participants were non-immunocompromised adults who had received a single dose of the vaccine. AEs were coded by using MedDRA terms and classified as expected (very frequent, frequent, infrequent) or unexpected.

The statistical analysis resorted to odds ratio (OR) and 95% confidence interval calculation in order to look for risk factors associated with the occurrence of post-vaccination AEs, by using simple and multivariate logistic regression.

Of the total number of individuals who had been vaccinated, 864 (37%) responded to the survey. Of these, 71% were female, 3% of which pregnant at the time of vaccination. Nineteen percent reported some kind of co-morbidity, and 73% sustained at least one AE. The most frequently reported AEs were expected and very frequent: local reactions (57%), myalgia (31%), fatigue (24%) and headache (19%). The **female** gender and the presence of **co-morbidity** were independent risk factors for the occurrence of at least one AE after vaccination. Of the respondents who had at least one AE, 34% needed drug treatment, 3% medical treatment. Three percent had to call in sick, and 2% went to the hospital. Although most vaccinated health professionals had at least one AE, only **8% were considered unexpected** and only **3% needed medical treatment**. No case of death or life-threatening condition was reported. The most frequently reported AEs were indeed expected and known to be very frequent.

The results above suggest that the benefit/risk ratio for the pandemic vaccine Pandemrix® is favourable, as described in other countries and other groups of adult subjects. Our results also match the adverse reaction reports received overall by Infarmed within the same time frame. It can therefore be suggested that the pandemic vaccine seems to show an acceptable safety profile in health professionals, and both the seriousness and the frequency of the AEs observed are as expected.

Joana Isabel Marques

Transpulmina® suppositories
Restrictions to use

Terpenic derivatives are obtained from natural plant compounds and include substances such as camphor, cineol (eucaliptol), niaouli, thyme, terpineol, terpene, citral, menthol, and pine, eucalyptus and turpentine essential oils. They are usually indicated for the treatment of mild acute bronchial conditions, namely productive and dry cough, and can be obtained without a medical prescription. In Portugal, only Transpulmina® (paediatric) suppositories contain the above substances.

A safety review of these medicinal products conducted by the CHMP has concluded that there is a risk of neurological reactions, especially seizures, in infants and small children, as well as a risk of ano-rectal lesions (pre-cancerous masses in the anus or rectum) in children with a previous history of such lesions.

Consequently, and according to EMA's recommendations, the use of suppositories containing terpene derivatives for the treatment of cough is **contraindicated** in children **younger than 30 months**, and in **children with a past history of epilepsy or of febrile seizures, or with a recent history of ano-rectal lesions**.

ADRs in the Literature…

Spironolactone, trimethoprim-sulfamethoxazole and hyperkalaemia

This Canadian study included patients aged 66 years or above receiving chronic treatment with spironolactone and admitted to hospital with hyperkalaemia within 14 days of receiving a prescription for either trimethoprim-sulfamethoxazole (TSM), amoxicillin, norfloxacin, or nitrofurantoin. Compared with amoxicillin, prescription of trimethoprim-sulfamethoxazole was associated with a marked increase in the risk of admission to hospital for hyperkalaemia (adjusted odds ratio 12.4, 95% confidence interval 7.1 to 21.6). The study suggested that approximately 60% of all cases of hyperkalaemia in older patients taking spironolactone and treated with an antibiotic for a urinary tract infection could have been avoided if trimethoprim-sulfamethoxazole had not been prescribed. Treatment with nitrofurantoin was also associated with an increased though smaller risk of hyperkalaemia (adjusted odds ratio 2.4, 1.3 to 4.6), but no such risk was found with norfloxacin.

The authors suggest that the combination of spironolactone with trimethoprim-sulfamethoxazole in older patients should be avoided when possible.

Antoniou, Toni et al. BMJ 2011; 343:d5228.

Interactions to keep in mind!

Patients taking the pill*

Oestrogens and progestagens are to a large extent metabolised by the liver, which explains the fact that most of the orally administered dose does not reach the general circulation. Their great dependency on hepatic metabolisation accounts for their high sensitivity to enzyme inducers whose concomitant use promotes the elimination of estrogen/progestagen agents, with an attendant significant risk of contraceptive failure. Under these circumstances it is probably best to resort to other, non-hormonal methods.

Risk of:

Decreased contraceptive effectiveness

- **Enzyme inducers** such as:
  - Antiepileptics such as carbamazepine, phenytoin, primidone
  - Topiramate
  - Rifampin
  - Antiretroviral agents (including some cytochrome P450 inhibitors) such as efevirenz, nevirapine, ritonavir
  - Hypericum

Orlistat (diarrhoea can decrease the absorption of oral contraceptives)

NB – Antibiotics in general and contraception: *Theoretically, modifying the gut flora could reduce the efficacy of oral contraceptives. The studies available however, do not suggest that antibiotics in general are associated with contraceptive failure. Therefore, special precautions do not seem to be justified.*

Antagonisation of other medicines by oral contraceptives

- **Anticoagulants (anti-vitamin K):**
  - Prefer mechanical methods or a low-dose progestagen, but avoid third-generation agents such as desogestrel or gestodene
- **Oral antidiabetic agents**
  - Glucose lowering therapy needs to be adjusted. Low-dose progestagens may be easier to manage.
- **Antihypertensive agents**
  Higher risk of cardiovascular events. Prefer a low-dose progestagen.
- **Lipid lowering agents**
- **Lamotrigine**
  - Its plasma concentration can be reduced by the association of ethinylestradiol with levonorgestrel. The dose of lamotrigine may have to be adjusted up to twice as much; alternatively, non-hormonal methods may have to be chosen.
- **Levothyroxine**
  - Reduction of the its plasma free fraction due to increased concentration of the transport protein thyroglobulin. The dose of levothyroxine may need to be adjusted.
- **Paracetamol and morphine**
  - Oestrogen/progestagen agents increase their elimination. Therefore, their dose may have to be increased for the same analgesic effect.

Increased effect of other medicines by oral contraceptives

- **Corticoids, theophylline, selegiline, ropirole, cyclosporin, tacrolimus**
  - Increased plasma concentrations
- **Benzodiazepines**
  - Increased or decreased elimination.

Potentiation of undesirable effects

- Thromboembolic phenomena
- High blood pressure
- Hyperlipidaemia
- Hyperglycaemia
- Hyperkalaemia
  - Medicines which raise blood potassium levels used concomitantly with the association ethynilestradiol + drospirenone

** Based on: la revue Prescrire*