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Editor's Notes

This quarter:

- special precautions with rosuvastatin due to risk of muscle toxicity;
- increased risk of cerebrovascular accidents associated with the use of the atypical antipsychotic drugs olanzapine and risperidone in elderly patients with dementia;
- good news on the safety profile of thiomersal used in the manufacture and preservation of vaccines for human use;
- nimesulide and hepatotoxicity again: an update;

A graph summary of the ADR reports received at the Pharmacovigilance Department in the first semester 2004 gives some insight into how the National Pharmacovigilance System is continuously by reports from all participants (health professionals, clinical trials, industry).

Rui Pombal

Rosuvastatin
muscle toxicity

Rosuvastatin is a selective, competitive HMG–CoA reductase inhibitor. In Portugal, Crestor® and Visacor® are authorised for marketing in the following dosages: 10 mg, 20 mg, 40 mg. The 10-mg dose is the only one actually marketed at the moment.

Muscle toxicity is a well-known adverse reaction to statins which, under rare circumstances, may cause life-threatening rhabdomyolysis. Cases of rosuvastatin associated rhabdomyolysis have been described worldwide, and recent international reviews of this issue have highlighted **increased risk with doses higher than 20 mg**, especially in patients with risk factors for rhabdomyolysis, or **simultaneously on fibrates**. Taking this into account, INFARMED has demed it necessary to send an alert to health professionals, and to change accordingly the Summary of the Product's Characteristics through an urgent procedure. The following are particularly relevant:

Every patient started on rosuvastatin should take an initial dosage of **10 mg once daily**. Fine tuning of dosage up to 20 mg should be done 4 weeks into therapy and only if necessary.

The 40-mg dose (which is not marketed in Portugal) should only be prescribed under specialist supervision and should be considered solely for patients with severe hypercholesterolaemia who have no known risk factors for rhabdomyolysis.

Further information at (in Portuguese):
http://www.infarmed.pt/pt/alertas/seguranca/09_06_2004_Circular_060_crescor.pdf

What do they stand for?!

ADR	Adverse Drug Reaction
CPMP	European Committee of Proprietary Medicinal Products
EMEA	European Medicines Evaluation Agency
IL	Information Leaflet
MA	Marketing Authorisation
SPC	Summary of the Product's Characteristics

How can I report an adverse reaction?

Postage Paid Card
yellow *(physicians),* **purple** *(pharmacists) or* **white** *(nurses)*

OR

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Portugal em Acção

Olanzapine
risk of stroke and increased mortality in elderly patients with dementia

Olanzapine (Zyprexa® and Zyprexa Velotab®) **is not indicated as an approved therapy in dementia associated with psychosis and/or behavioural symptoms**. Recently, the EMEA Committee on Proprietary Medicinal Products has been informed on new data from clinical trials on **elderly patients with dementia**. Data analysis has revealed that, compared to placebo, the **mortality rate** of patients treated with olanzapine was **twice as high**. Furthermore, the incidence of adverse **cerebrovascular events trebled** in patients taking olanzapine, whilst the efficacy of the latter was not demonstrated in this group of patients.

In order to reflect these new safety data, the SPC and Information Leaflet of olanzapine have been revised. Thus the SPC shall henceforth include the following information in the corresponding sections:

4.4 **Warnings and special precautions of use**

Olanzapine is not approved for the treatment of dementia associated with psychosis and/or behavioural symptoms, and its use in this group of patients is not recommended, due to increased mortality and increased risk of cerebrovascular accidents. In placebo controlled clinical trials (6-12 weeks) in elderly patients (mean age 78 years) with dementia associated with psychosis and/or behavioural symptoms, patients treated with olanzapine showed an incidence of death twice as high as that of patients treated with placebo (3.5% vs.1.5%, respectively). The increased number of deaths was not associated with the dose of olanzapine (mean daily dose 4.4 mg), nor with duration of treatment.

Risk factors that may predispose this patient population to increased mortality include age greater than 65 years, dysphagia, sedation, poor nutrition, dehydration, pulmonary conditions (e.g. aspiration or non-aspiration pneumonia), and concomitant use of benzodiazepines. The number of deaths however, was greater in patients treated with olanzapine than in patients on placebo, independently of the above risk factors.

In the same clinical trials, cerebrovascular adverse events were reported (e.g.: stroke, TIA), including fatal cases. Their incidence was three times higher in patients on olanzapine when compared to patients treated with placebo (1.3% vs. 0.4%, respectively). All patients treated with olanzapine or with placebo who sustained an adverse cerebrovascular event had pre-existing risk factors. Age greater than 75 years and vascular/mixed type dementia were identified as risk factors for cerebrovascular events in association with treatment with olanzapine. The effectiveness of olanzapine was not demonstrated in these trials.

4.8 **Undesirable effects**

In clinical trials in elderly patients with dementia, treatment with olanzapine was associated with an increased number of deaths and of cerebrovascular adverse events, in comparison with placebo (see also 4.4). Very frequent (>10%) adverse effects associated with the use of olanzapine in this group of patients were gait disturbances and falls. Pneumonia and urinary incontinence were frequent (1-10%).

Further information at the INFARMED and EMEA sites:

http://www.infarmed.pt
http://www.emea.eu.int/

Risperidone
risk of stroke in elderly patients with dementia also increased

Risperidone (Belivon®, Belivon Quicklet®, Belivon Consta®, Risperdal®, Risperdal Consta®, and Risperdal Quicklet®) is an atypical antipsychotic agent which, in Portugal, is authorised for the treatment of behavioural symptoms in patients with dementia. INFARMED has been informed on new important safety data pertaining to the use of risperidone in dementia. These data from clinical trials have demonstrated an **increased risk of cerebrovascular accidents** (stroke/TIA) in **elderly patients with dementia** taking risperidone, similarly to another atypical antipsychotic, olanzapine *(see above)*. The mechanism underlying the increased risk of cerebrovascular accidents has not been fully explained. On the other hand, currently available data are not sufficient to decide whether there are any differences in the risk identified between atypical and conventional antipsychotics.

Given the seriousness of the above reactions, INFARMED has recommended that physicians give risperidone with special **caution to patients at increased risk (diabetes, hypertension, arrhythmia, smoking, etc.), or with a past history of cerebrovascular accident (stroke or TIA).**

Thiomersal

favourable risk-benefit profile for vaccines

Thiomersal is an organomercurial, antimicrobial compound, which is usually used for vaccine manufacturing at its initial steps, or as a preservative agent. Thiomersal's antimicrobial properties are ascribed to **ethylmercury**, which results from thiomersal's separation into ethylmercury and thiosalicylate.

EMEA and INFARMED already released safety information in 1999 and 2000 concerning the fact that, although there is no evidence of untoward effects of thiomersal contained in vaccines, apart from hypersensitivity (allergic) reactions, the use of this compound or of other mercurial compounds should be avoided in the manufacture of vaccines, especially single dose vaccines. Since then, several vaccines authorised within the European Union have been withdrawn, or the quantity of thiomersal in their composition has been reduced. However, former studies evaluating risks associated with the use of ethylmercury were actually based on data from methylmercury, taking for granted that both compounds' safety profile should be similar. **Recent epidemiological studies have demonstrated that there is no association between immunisation with thiomersal containing vaccines and neurodevelopmental disorders, such as speech disorders or autism. New data indicate that in children, ethylmercury is rapidly excreted**, therefore with a pharmacokinetic profile very different from that of methylmercury. This suggests that ethylmercury is probably not as toxic as previously thought.

Bearing this in mind, the EMEA Committee on Proprietary Medicinal Products has concluded that:

- The latest epidemiological studies have demonstrated that there is no association between immunisation with thiomersal-containing vaccines and neurodevelopmental disorders.
- The benefits of immunisation with thiomersal-containing vaccines far outweigh risks (should they exist at all).
- The use of organomercurial compounds in manufacture is sometimes necessary. In this case, residual levels may be found in the final product. However, efforts should be kept up to reduce exposure to mercury by producing vaccines with the lowest possible levels of organomercurial preservatives.
- Thiomersal can be used in multidose regimes should the use of preservatives be necessary.
- Labelling of vaccines containing thiomersal (or other preservatives) should state its presence within its composition, and the SPC and IL should include warnings on the risk of hypersensitivity to thiomersal or to other preservatives.

Further information at:

http://www.emea.eu.int/pdfs/human/press/pus/119404en.pdf
http://www.emea.eu.int/pdfs/human/press/po/157800en.pdf
http://www.emea.eu.int/pdfs/human/press/pus/2096299EN.pdf

Nimesulide

Safety Profile Reassessment – Current Status

Nimesulide is a non-steroidal anti-inflammatory drug (NSAID) whose pharmacological action is due to preferential inhibition of cyclooxygenase 2, with reduction of prostaglandin production. It has been authorised in Portugal since 1985, and is also authorised in other member states. It is now marketed in over fifty countries.

The risk of nimesulide associated hepatic adverse reactions is probably this medicine's main safety issue, and this has been formerly discussed in this Bulletin in more than one occasion. The idiosyncratic nature of these reactions makes it hard to pinpoint associated risk factors, and therefore the definition of individual vulnerability profiles. In 1999 INFARMED, following an assessment of the drug's safety profile based on spontaneous reports received and on published literature, concluded that:

– the risk-benefit ratio of this medicine in paediatric age groups was unfavourable, thus leading to **discontinuation of paediatric indications** of nimesulide in Portugal;

– information (SPC and IL) approved for nimesulide should be reviewed in order to reflect the safety data that emerged from the above assessment. The MA holders thus made a full review which resulted in restriction of indications (namely by suspending the indication in pyrexia), as well as in inclusion of new contraindications, warnings, interactions, and undesirable effects.

In March 2002, the Finnish Medicines Agency, given the available data and an increased frequency of adverse liver reactions (from asymptomatic liver enzyme elevation to liver failure requiring transplantation), and considering this medicine's indications for conditions of only relative severity, has concluded that its risk-benefit ratio is unfavourable and has thus suspended its MA. Spain followed suit in May 2002. Later, based on a detailed reassessment called forth by the EMEA, the European Commission decided in April 2004 to keep this medicine in the market, though making it compulsory to scrupulously follow the information contained in the harmonised SPC and IL, which include the new data emerging from the above-mentioned reassessment process.

The main conclusions arising from the safety reassessment conducted by the European expert committee are summarised below:

EFFECTIVENESS

In terms of therapeutic indications, it has been demonstrated that the risk-benefit ratio of nimesulide in oral preparations is favourable in the following only:

– treatment of acute pain;
– treatment of symptomatic osteoarthritis in its algic phase;
– primary dysmenorrhoea.

SAFETY

As a general rule, this medicine should be used for the **shortest possible periods of time**, following its therapeutic indications. Nimesulide's maximum daily dose should be **100 mg twice daily**, orally.

PAEDIATRIC USE

According to current evidence, there are no data that justify its use in children. It is therefore **contraindicated in children younger than 12 years**.

GASTROINTESTINAL SAFETY

The most frequent adverse reactions associated with the use of non-steroidal anti-inflammatory drugs are gastrointestinal, and range from dyspepsia and other minor complaints to more severe, potentially fatal reactions, such as ulcers, haemorrhage, and perforation. Epidemiological data indicate that the occurrence of serious gastro-duodenal complications (haemorrhage and perforation) is ten times higher that that of liver toxicity. Data available from clinical trials and pharmacoepidemiological data comparing nimesulide to other non-steroidal anti-inflammatory agents, indicate that nimesulide shows an acceptable gastrointestinal safety profile, especially in treatments of short duration.

Results from a recent multicentre, case-control study conducted in eighteen hospitals in Spain and Italy, in which 2,813 cases of upper GI haemorrhage due to gastric or duodenal lesions were assessed, showed that 38% of cases were associated with NSAID use. The individual relative risk for each NSAID was calculated. It was estimated that the risk associated with nimesulide was low (3.2; 95% CI: 1.9, 5.6) compared to other medicines within this pharmacological class. Thus for instance, the highest relative risk was associated with ketorolac (24.7; 95% CI: 8.0, 77.0), and the lowest to celecoxib (0.3; 95% CI: 0.03, 4.1).

LIVER TOXICITY

The mechanism of hepatotoxicity associated with both nimesulide and other NSAIDs has been extensively researched, though with no final and clear conclusions. However, a set of factors that seem to contribute towards nimesulide's liver toxicity has been identified, namely: genetic susceptibility, drug interactions, pre-existing concomitant conditions (such as liver failure), mitochondrial dysfunction, hypersensitivity.

The **Finnish** and the **Spanish adverse reaction reporting systems** have been analysed in depth, and do indeed suggest that nimesulide has a **risk of liver toxicity higher than that of other NSAIDs**. This however, has not been confirmed by any other member state where this medicine is being marketed. Completely satisfactory reasons for differing reporting rates have not been found. In fact, based on the assessment of reporting systems worldwide, as well as on data from clinical trials and on epidemiological data, the frequency of serious hepatic reactions seems to be similar to that of many other NSAIDs.

In Portugal, nimesulide was already **contraindicated in patients with liver failure**, and is currently also contraindicated in patients with a history of liver toxicity associated with nimesulide. In patients who come down with symptoms compatible with liver injury during treatment with nimesulide, or who show persistent liver enzyme elevations, treatment should be discontinued, and they should not be re-exposed to nimesulide. **Concomitant administration of nimesulide with hepatotoxic medicines, as well as alcohol abuse, should be avoided**.

Knowledge on the safety and efficacy of medicines and their position within the therapeutic armamentarium varies with time, therapeutic experience and experimentation. Spontaneous reporting systems, active and permanent market vigilance, and international information exchange, allow for multiple efforts to be brought together, in order to find consensus answers to safety and effectiveness questions, whenever a potential signal is detected.

Paula Roque

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- Traversa G, Bianchi C, Da Cas R, Abraha I, Menniti-Ippolito F, Venegoni M. Cohort study of hepatotoxicity associated with nimesulide and other non-steroidal anti-inflammatory drugs. BMJ. 2003;327(7405):18-22.
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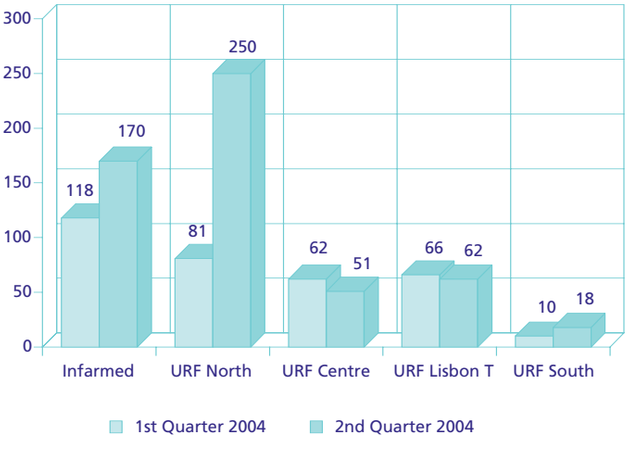
The National Pharmacovigilance System day in day out.

ADR reports in the first half of 2004.



URF: Regional Pharmacovigilance Unit; TV: Tagus River Valley.