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## Editor's Notes

We start off the Boletim's ninth year with an overview of ADR reports received by the National Pharmacovigilance System throughout 2004. From INFARMED's 2005 Annual Conference a summary of online sources of information including some of the currently most authoritative, accessible, and relevant for a target audience of health professionals.

In 2005, on account of its current risk-benefit assessment, a medicine which has long been traditionally used off label is now discontinued: thioridazine.

***Rui Pombal***

## ADR Reports 2004

| ADR Total | Total | Originators | | | |
|---|---|---|---|---|---|
| | | Physicians | Pharmacists | Nurses | Industry |
| ADR reports received | 1469 | 778 | 252 | 106 | 333 |

| Reports of serious ADRs | Total | Originators | | | |
|---|---|---|---|---|---|
| | | Physicians | Pharmacists | Nurses | Industry |
| Serious ADR reports received | 985 | 427 | - | - | 313 |

| Clinical Trials | Expected | Total | Serious |
|---|---|---|---|
| TOTAL reports received | NA | 316 | 293 |

## What do they stand for?!

**ADR** Adverse Drug Reaction
**CHMP** Committee for Medicinal Products for Human Use
**EMEA** European Medicines Evaluation Agency
**IL** Information Leaflet
**MA** Marketing Authorisation
**SPC** Summary of the Produt's Characteristics

## How can I report an adverse reactio

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

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

**OR**

**National Pharmacovigilance Centre**
Tel: 217 987 140 - Fax: 217 987 155
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**Northern Regional Pharmacovigilance Unit**
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Tel: 217 802 120 - Fax: 217 802 129
E-mail: ufs@infarmed.pt

**Southern Regional Pharmacovigilance Unit**
Tel: 217 971 340 - Fax: 217 971 339
E-mail: urf@ff.ul.pt

## Thioridazine (Melleril®) discontinued

Thioridazine is an antipsychotic indicated for the treatment of adult patients with chronic schizophrenia, or with acute exacerbations which do not adequately respond to therapy with other antipsychotics, either on account of insufficient effectiveness, or of their adverse effects. Thioridazine is marketed in Portugal under the trademark name Melleril® .

Thioridazine's risk-benefit ratio has been assessed following reports of **serious cardiac arrhythmia**. Thioridazine was shown to have an unfavourable safety profile due to QT-interval prolongation. This is not sufficiently counterbalanced by the specificity of its therapeutic indications.

This conclusion has been reached mostly based on the following:
- thioridazine inhibits cardiac calcium channels with an attending effect on cardiac repolarisation;

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Portugal em Acção

- thioridazine is associated with dose-dependent QT-interval prolongation;
- available data on the effects of thioridazine on **QT-interval prolongation and risk of sudden death** consistently show that these adverse reactions are more frequent in patients treated with this medicine when compared with equipotent doses of other antipsychotics.

The MA holder of Melleril® has decided to permanently discontinue this medicine worldwide as of June 2005. Health professionals, namely physicians, have been informed and advised to substitute this therapy in patients currently on thioridazine, and to abstain from starting new treatments with thioridazine

***Paula Roque***


- Appleby L, et al. Sudden unexplained death in psychiatric in-patients. Br J Psychiatry 2000 May;176:405-6.
- Hancox JC, et al. Psychotropic drugs, HERG, and the heart. Lancet 2000 Jul; 356(9227):428.
- Hartigan-Go K, et al. Concentration-related pharmacodynamic effects of thioridazine and its metabolites in humans. Clin Pharmacol and Ther 1996; 60:543-53.
- Reilly JG, et al. QTc-interval abnormalities and psychotropic drug therapy in psychiatric patients. Lancet 2000; 355:1048-52
- Reilly JG; et al. Thioridazine and sudden unexplained death in psychiatric in-patients. Br J Psychiatry 2002 Jun;180:515-22.
- Timell AM. Thioridazine: re-evaluating the risk-benefit equation. Annals of Clinical Psychiatry 2000; 12:147-51.


## Combined Antiretroviral Therapy
## immune reactivation syndrome

In HIV-infected patients, susceptibility to opportunistic infections becomes usually more pronounced as the number of CD4+ lymphocytes drops below 200 cells /mm$^3$. It has sometimes been seen however, that an inflammatory response to residual antigens from opportunistic agents may occur in patients who are being started on effective antiretroviral association therapy with good treatment response and marked improvement in the number of CD4+ lymph cells. Although a mechanism has not yet been clearly defined, it is thought that this corresponds to clinically silent conditions being reactivated by the inflammatory response induced by CD4+ memory lymph cells. The latter increase during the first immunity recovery phase as effective antiretroviral association therapy is started.

In most cases one cannot predict the consequences of an eventual immune reaction induced by an increase in CD4+ lymph cells, which makes it especially important to detect and diagnose these inflammatory reactions as early on as possible. For this reason, a description of this immune reactivation phenomenon has been included in the SPCs of all medicines used as antiretroviral therapy.

**4.4 – Warnings and special precautions of use**
Upon starting treatment with effective antiretroviral association therapy in HIV-infected patients and in severe immune deficiency patients, an inflammatory reaction to residual or subclinical opportunistic pathogen antigens may occur, giving rise to new clinical conditions, or to worsening of pre-existing symptoms. These reactions have generally been observed in the **first few weeks or months into therapy.** Some relevant examples of such reactions include: cytomegalovirus vitritis/retinitis, febrile syndromes associated with generalised and/or focal mycobacterial infection, and Pneumocystis carinii pneumonia. **Any emerging inflammatory symptom should be assessed, and its treatment started whenever necessary.**

**4.8 – Undesirable effects**
Upon starting treatment with effective antiretroviral association therapy in HIV-infected patients and in severe immune deficiency patients, **an inflammatory reaction to residual or subclinical opportunistic pathogen antigens** may occur (see section 4.4).

***Isabel Brito Afonso***


- Hermsen ED, Wyn HE, Mcnabb J. Discontinuation of prophylaxis for HIV – associated opportunistic infections in the era of highly active antiretroviral therapy. Am J Health-Syst Pharm 2004; 61(3):245-256.


## Nucleoside/Nucleotide Analogue
## Reverse Transcriptase Inhibitors
## mitochondrial toxicity in children

Nucleoside/nucleotide analogue RTIs have been shown to cause mitochondrial dysfunction of varying severity, both *in vitro* and *in vivo*. Cases have been reported of seronegative children exposed to nucleoside/nucleotide analogues *in utero* who developed clinical symptoms of mitochondrial dysfunction. The most frequently reported ADRs were haematological (anaemia, neutropoenia), and metabolic (hyperlactaemia, hyperlipasaemia). These effects are often transient. Neurological dysfunction manifesting itself at a later stage has also been reported, including hypertonia, seizures, and abnormal behaviour. It is not known whether the neurological effects are transient or permanent.

**Any child who has been exposed to nucleoside/nucleotide analogues *in utero*, even if HIV-negative, should be closely followed up.** In case of relevant signs or symptoms, a possibility of mitochondrial dysfunction should be extensively investigated. The above does not in any way change current national guidelines on the use of antiretroviral therapy in pregnant women to prevent vertical transmission of HIV.

***Isabel Brito Afonso***


- Blanche S, Tardieu M, Rustin P, et al. Persistent mitochondrial dysfuction and perinatal exposure to antiretroviral nucleoside analogues. The Lancet, 1999 ; 354

# Online Sources of Information in Pharmacovigilance

## Authorities

www.emea.eu.int/htms/human/press/pus.htm

www.who-umc.org

www.eudravigilance.org
EU legislation and guidelines

Human Medicines
Choose topics here...
MAIN INDEX
- Press Office
- Public Statements
- Special Topics
- Summaries of Opinion
- List of Authorised Products (EPARs)
- Orphan Medicinal Products
- Product Safety Announcements
- Marketing Authorisation Withdrawals and Suspensions
- Pharmacovigilance
- Referrals
- Guidance Documents
- Application Procedures
- Parallel Distribution
- Plasma Master File
- Inspections
- Herbal Medicinal Products

The FDA Safety Information and Adverse Event Reporting Program

www.fda.gov/medwatch

## Online Pharmacovigilance Bulletins 1

www.tga.gov.au/adr/aadrb.htm

www.medsafe.govt.nz/profs.htm

Monitoring safety and quality of medicines: Current Problems in Pharmacovigilance

http://medicines.mhra.gov.uk/ourwork/monitorsafequalmed/currentproblems/currentproblems.htm

## Online Pharmacovigilance Bulletins 2

ttp://afssaps.sante.fr/htm/5/indbphar.htm

www.icf.uab.es/informacion/boletines/bg/asp/bg_e.as

www.madrid.org/sanidad/farmacia/farmacovigi/

www.cfnavarra.es/BIF/

## Interactive databases and specialised search engines 1

www.toxnet.nlm.nih.gov

Search in parallel on the following databases:
Toxicology Bibliographic Info,
Developmental and Reproductive Toxicology,
Hazardous Substances Databank, Integrated Risk Information System, Internat'l Toxicity Estimates for Risk, Mutagenecity, ...
Chemical Synonyms

## Interactive databases and specialised search engines 2

PNEUMOTOX ON LINE

Service de Pneumologie
et Réanimation Respiratoire,
CHU de Dijon - FRANCE

www.pneumotox.com

III : Pulmonary hemorrhage

III (a) Alveolar hemorrhage

Gliclazide*

Patterns : V (b)* : Eosinophilic pleural effusion

1. Tzanakis N, Bouros D, Siafakas N. Eosinophilic pleural effusion due to gliclazide. Respiratory Medicine 2000; 94: 94

## Interactive databases and specialised search engines 3

www.biam2.org

Search by:
INN
Molecule
Chemical class
Pharmacological properties
Effects intended
Indications
Side effects (incidence)
Effects in offspring
Pharmacological addiction
Special precautions
Contraindications

www.orphanet.net

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**Pharmacovigilance Bulletin (Boletim)** since 1997

**Other related sources**
information and documentation for professionals and the general public, databases, and search engines

**Medicines and Health Products Information Centre (CIMI)**

Information for health professionals, general public, and other sector agents, on medicines, health products, and related activities.

Medicines hotline: 800 222 444 Phone: +21 798 7373 Fax: +21 798 731 cimi@infarmed.pt

**Technical and Scientific Documentation Centre (CDTC)**

Technical and sceintific support to all internal and external users by means of a specialised pharmacy, medicine and health products document database

Library

On-site searches on the following databases

DrugDex, Drug-Reax, Martindale; OECD Health Data; HEED; The Cochrane Library; ACP MEDICINE

Phone: +21 798 7171 / 5287 / 7173 Fax: +21 798 7316 cdtc@infarmed.p


Pombal R. Fontes de Informação em Farmacovigilância in Conferência Anual do INFARMED 2005-1-25.

## Dinoprostone and Oxytocin
### disseminated intravascular coagulation

Dinoprostone (prostaglandin E2) and oxytocin have been widely used to promote softening of the uterine cervix and to stimulate uterine activity. In 1999 nine cases of post-partum disseminated intravascular coagulation (DIC) associated with dinoprostone were reported in Spain, one of which was fatal. This event, though rare, is directly related to labour induction. In Portugal, five ADRs of dinoprostone-associated DIC had been reported until as late as 2002.

Following the above cases, a scientific committee was appointed in Spain to design and conduct a retrospective, case-control study to assess this possible signal. The results obtained seem to support the hypothesis that pharmacological induction of labour is associated with an **increased risk of post-partum DIC,** either with dinoprostone (RR 6.7; 95% CI: 1.7 – 26.5), or with oxytocin (RR 8.4; 95% CI: 1.4 – 50.9), whatever the reason for induction. However, using oxytocin for the induction of labour in cases of uterine inertia, either following previous induction or not, had a protective effect against DIC. This could be explained by shorter duration of labour.

Identified **risk factors** were: age of the pregnant woman (35 years or older), complications during pregnancy, gestational age greater than 40 weeks, and use of ante- and intrapartum medication. These risk factors are independent of one another.

INFARMED has decided to include this item of safety information in the SPCs.

***Isabel Brito Afonso***

- De Abajo FJ, Meseguer CM, Antiñol G, García Rodríguez LA, Montero D, Castillo JR, Torelló J. Labour induction with dinoprostone or oxytocin and postpartum disseminated intravascular coagulation: a hospital-based case-control study. American Journal of Obstetrics and Gynecology. In Press.

## Injectable Sodium Fluorescein
### hypersensitivity reactions

INFARMED has recently been informed by EMEA on an increase in the number and severity of hypersensitivity reactions to injectable sodium fluorescein. This matter is undergoing thorough assessment. Although INFARMED has not received any ADR reports involving injectable sodium fluorescein, the following reminder is in order:

- Hypersensitivity reactions, although unpredictable, are more frequent in patients with **previous reduced tolerance** (nausea and vomiting) to this medicine, and who have a **past history of allergy.**
- Patients on **beta-blockers, including eye drops,** are considered to be at risk, since in case of shock or hypotension, adrenaline and measures to revert haemodynamic compromise are not as effective.
- In view of the risk of hypersensitivity, a detailed questionnaire (history of allergy, asthma, concurrent therapy, especially beta-blockers) should always be made to the patient before the exam. **Following the exam the patient should be placed under medical surveillance for at least 30 minutes.**
- Due to the risk of this type of reactions, the site where the examination is conducted must always be fitted with **emergency resuscitation equipment** as described in the medicines information leaflet.
- In patients who have been identified as being at risk, the exam's diagnostic relevance should be weighed against the patient's risk. These patients may benefit from previous administration of medicines to prevent hypersensitivity reactions. Still, serious adverse reactions cannot be prevented with absolute certainty.

***Alexandra Pêgo***

## Errata

1. In Volume 8, Nº. 3, 3rd Quarter 2004 (page 4), the 12th line in Table II should read: "Eustidil® - Nasal spray suspension - Fluticasona propionate - 0.5mg/g", instead of 50mg/g., which was incorrect.