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From the Editor

Intravenous administration of medicines requires special care in preventing potential adverse reactions which are characteristic of this route. The similar ADR profile of tibolone and other hormonal replacement therapy agents is also under the spotlight this quarter. An increased risk of fractures and of clinically significant hypomagnesaemia should be borne in mind when proton pump inhibitors are used for prolonged periods of time and/or in high doses.

In the usual literature review section an extensive review is highlighted on the probable usefulness of probiotics in preventing a common ADR – antibiotic-associated diarrhea.

The page 2 article on ADR reports in the year 2011 illustrates another step forward in the development of the Portuguese National Pharmacovigilance System. On the other hand, barriers to reporting still impact on the evolution of the system. This is mirrored in an interesting study from Northern Portugal on knowledge and attitudes of nurses concerning ADR reporting.

*The various **factors underlying underreporting** by health professionals can broadly be divided into personal and professional characteristics of the care providers, and their knowledge and attitudes.[1] **Inman** sums up these factors in seven types aptly called "seven deadly sins", and which can be fitted into two major categories:[2]*

- ***Attitudes relating to professional activities**:*
- *financial incentives (rewards for reporting);*
- *legal aspects (fear of litigation or enquiry into prescribing costs);*
- *ambition to compile or publish a personal case series.*
- ***Problems associated with ADR-related knowledge and attitudes:***
- *complacency (the belief that very serious ADRs are well documented by the time a drug is marketed);*
- *diffidence (the belief that reporting an ADR would only be done if there was certainty that it was related to the use of a particular drug);*
- *indifference (the belief that a single case an individual professional might observe could not contribute to medical knowledge);*
- *ignorance (the belief that it is only necessary to report serious or unexpected ADRs).*

To these types one can add lethargy – procrastination and disinterestedness in reporting or lack of time to find a report card and other excuses by health professionals.

According to Lopez-Gonzalez,[1] incentives, fear, and ambition for publication are factors of less relevance than the remainder. On the contrary, this author signals insecurity in determining a causality link between ADRs and medicines as another paramount factor.

How can I report an adverse reaction?

- **Postage Paid Card**
- **Also online at:**
  www.infarmed.pt/portal/page/portal/INFARMED/MEDICAMENTOS_USO_HUMANO/FARMACOVIGILANCIA/NOTIFICACAO_DE_RAM
- **ADR Portal (Portal RAM) (from July, 2012)**
- **OR**

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There can also be differences from one country to another in what concerns the relative weight of factors contributing towards underreporting.[3] Most factors however are consistently the same. All of them deserve to be addressed for pharmacovigilance systems to mature further.

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[1] Lopez-Gonzalez E, Herdeiro MT, Figueiras A: Determinants of under-reporting of adverse drug reactions: a systematic review. Drug Saf 2009, 32:19-31.

[2] Inman WH: Attitudes to adverse drug-reaction reporting. Br J Clin Pharmacol 1996, 41:433-435.

[3] Perceptions of doctors to adverse drug reaction reporting in a teaching hospital in Lagos, Nigeria. Oshikoya KA, Awobusuyi JO. BMC Clin Pharmacol. 2009 Aug 11;9:14.

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

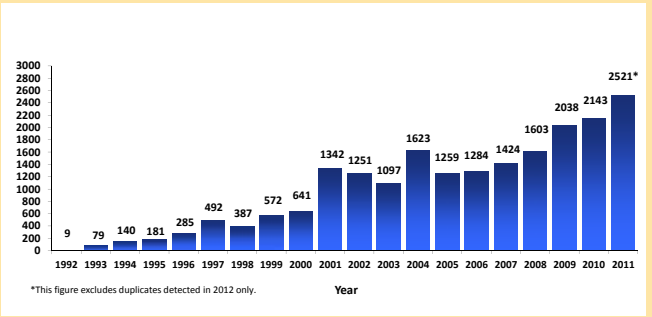
BOLETIM'S ONLINE INDEX AT:
http://www.infarmed.pt/portal/page/portal/INFARMED/ENGLISH/PHARMACOVIGILANCE_BULLETIN/ONLINE_INDEX

INDEX CARD | **Director:** Alexandra Pego **Editor:** Rui Pombal **Assistant Editor:** Cristina Rocha **Contributors:** Ana Araújo, Catarina Fernandes Costa, Cristina Mousinho, Fátima Bragança, Fátima Hergy, Inês Clérigo, Joana Oliveira, Leonor Nogueira Guerra, Magda Pedro, Margarida Guimarães, Pedro Marques Silva **Publishing Assistant:** Inocência Pinto **Advisory Board:** Conselho Directivo do INFARMED, I.P.; Comissão de Avaliação de Medicamentos **Publisher:** 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, Tel.: 217 987 316, correio electrónico: infarmed@infarmed.pt **Design and production:** Letras&Sinais,Comunicação e Imagem, Lda. **Printing:** Rainho&Neves,Lda. **Legal Deposit:** 115 099/97 **ISSN:** 0873-7118 **Print Run:** 49 000 (Portuguese)

Adverse Drug Reactions reported in Portugal in 2011

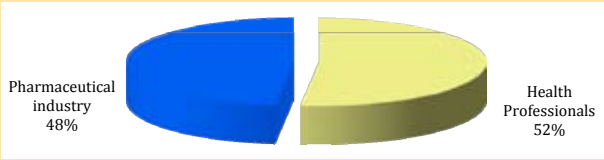
The number of cases of ADRs reported to the Portuguese National Pharmacovigilance System has been steadily growing from its inception (June 1992) to the present. Within the 1992-2011 period, a total of 20,371 spontaneous (i.e., not from clinical trials) ADR reports have been received (chart 1).

Chart 1. ADR cases entered in the National Pharmacovigilance System
N=20.371



Looking more closely into the ADR reports received in the year 2011, one can see that as many as 2,521 cases were reported to Infarmed. Of these, 1,305 were sent in directly by health professionals and the remainder by MA Holders – see chart 2. In 2011, **direct reports from health professionals increased** in such a way that their proportion nearly equalled that of the "pharmaceutical industry", whereas in 2010 MA Holders had accounted for over 63% of all reports.

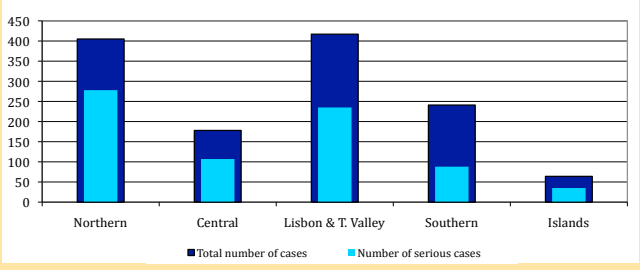
Chart 2. Relative frequency of spontaneous reports received by the National Pharmacovigilance System in 2011 directly from health professionals and from the pharmaceutical industry (N=2521)



In terms of seriousness, 1,919 cases (**76%**) were deemed serious by the reporter. This was similar to 2012 (75%) and actually expected since, a few exceptions notwithstanding, MA Holders are legally required to immediately report serious ADRs only. This also explains why reports from MA Holders include as much as 97% of serious cases, compared to 57% of serious cases coming in directly from health professionals.

Concerning the latter, Chart 3 shows how the reports were distributed both in terms of seriousness and of geographical origin. Reporting in both the Lisbon and Tagus Valley and the Southern Portugal regions went up from 29 to 32 percent, and from 13 to 18 percent, respectively. The islands of the Azores and Madeira remained at 5% of the total of reports, whereas the Northern and Central Portugal regions decreased slightly from 34 to 31 percent and from 19 to 14 percent, respectively.

Chart 3. Absolute frequency of the total of cases and of serious cases of ADRs directly submitted to the National Pharmacovigilance System by health professionals in 2011 (N=1,305)



However, taking into account that the total number of direct reports from health professionals increased from 1,091 in 2012 to 1,305 in 2011, a lower proportion does not necessarily mean that a slump in absolute numbers has occurred; that was not in fact the case in the Northern region, which saw a rise in the number of cases entered.

As for the "health professionals" origin only, in 2011 **pharmacists** accounted for most reports (44%), followed by **physicians** (41%) and **nurses** (15%). This is new in relation to most former years, in that only in 2009 had there been a greater proportion of ADRs directly reported by pharmacists. The distribution by branch/specialty is shown in Tables I and II.

Table I. Absolute frequency of cases from pharmacists by branch (N=571)

Pharmacist (Branch)	% of total Pharmacists
Community	64
Hospital	36

Table II. Absolute frequency of cases from physicians by specialty (N=537)

Physician (Specialty)	% of total Physicians
General/Family Medicine	15
Other specialties	82
Unknown	3

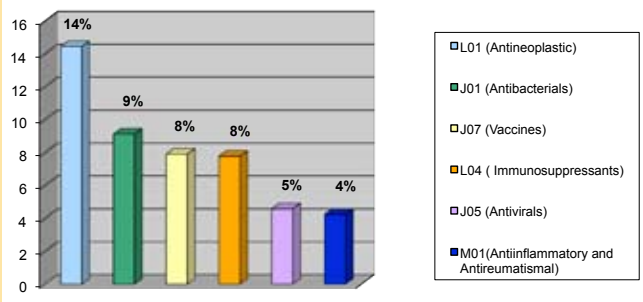
The categories of adverse reactions reported in 2011 have been analysed for organ systems involved. These groups correspond to a MedDRA (Medical Dictionary for Regulatory Activities) "Primary SOC (System Organ Class) term" hierarchical level analysis.

For each case, ADRs belonging to a same SOC were counted only once, since often a single case will include several ADRs which are nothing but a detailed description of a single nosological entity. Counting each descriptor per se one by one would produce repeated SOCs for the same case.

The sum total of the number of ADRs (from all cases) which match distinct SOCs was 2,469 "episodes". The following SOCs were prominent: **General disorders and administration site conditions** ("Genrl" – 20% – mostly reactions to vaccines and injected medicines in general), **Skin and subcutaneous tissue disorders** ("Skin" - 20% as well – this segment owing a great share of its weight to frequently reported protean hypersensitivity reactions), **Gastrointestinal disorders** ("Gastr" – 12%), and **Nervous system disorders** ("Nerv" – 10%). Together the above SOCs totalled 62%, as opposed to 38% from the remaining twenty-two.

Finally, in what concerns the suspected medicines or interactions from the 2,521 ADR cases, the six most represented ATCs (Anatomical Therapeutic Chemical) groups in 2011 corresponded to 48% of reports (Chart 4).

Chart 4. Suspected or interacting medicinal product ATCs most represented – relative frequency (N=1428; 48% of the total)



Leonor Nogueira Guerra, Inês Clérigo, Fátima Hergy

Study on the Attitudes of Nurses towards Spontaneous ADR Reporting

Introduction: ADRs are an important, worldwide recognised cause of morbidity and mortality. Spontaneous reporting systems are essential for the early detection of problems to do with the use of medicinal products, underreporting on the part of health professionals being their main limitation. It is estimated that only ten percent of all ADRs are reported to the medicines agencies. Nurses make up a group of professionals which can play a significant role within the ADR reporting system.

Objectives: To identify nurses' attitudes and knowledge which can be associated with ADR underreporting.

Methods: Case-control study involving nurses working in the Northern Portugal region. Cases (n=265): nurses who had sent in at least one ADR report to the Northern Portugal Regional Pharmacovigilance Unit until 2010. Controls (n=1060): random stratified sample of non-reporting nurses; randomisation was carried out proportionally to the number of nurses in each district within the region. A mailed self-administered questionnaire was applied. The statements used in the questionnaire were essentially based on the attitudes proposed by Inman for underreporting. Logistic regression analysis was used to measure the influence of the above attitudes on spontaneous ADR reporting.

Results: Of the total of 1,325 questionnaires sent out to the selected sample, 263 filled out questionnaires and 39 void questionnaires were received (response rate, 20.5%). The results showed that nurses working in community health centres/practices have a 14-fold higher risk of reporting ADRs than those working in hospitals. As for knowledge and attitudes, the risk of reporting increases (a) two-fold for "One ADR reported by a single nurse does not add much to scientific knowledge", (b) three-fold for "I would report more if the system were simpler", and (c) two-fold for "I do not know what becomes of the data provided in the reporting form".

Conclusions: Nurses' knowledge and attitudes influencing ADR reporting vary. According to this study, **not knowing** the pharmacovigilance system, the myth of its **complexity**, and **indifference**, seem to be the reasons most hindering ADR reporting among nurses. Educational interventions whose design is based on the attitudes identified and taking into account varying work settings may help to improve the problem of underreporting within this professional group.

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Tibolone Risk Reassessment

A case-control study has been conducted on the General Practice Research Database (GPRD) to investigate the effect of the use of tibolone and other hormonal therapies on the incidence of venous thromboembolism (VTE).[1] Data from clinical trials and post-marketing cases have also been assessed. The GPRD study indicates that there does **not** seem to be any **increased risk of VTE** associated with short-term use. However, these limited data do not allow for this risk to be altogether excluded.

The data from an epidemiological study in the GPRD have also been assessed for the risk of myocardial infarction. [2] The number of patients taking tibolone in this study was too small for any differences to be detected. Although the data are insufficient for a robust estimation of any possible risks, they do suggest tibolone does **not** afford **protection against myocardial infarction**.

Concerning **breast and ovarian cancers**, the results of the Million Women Study (MWS) were reviewed.[3] In this study, five years of hormonal replacement therapy (HRT) were associated with one additional case per 2,500 users. Relative risk for ovarian cancer with tibolone was **similar** to the risk with other types of hormonal replacement therapy (HRT).

Finally, a reanalysis of WHI (Women's Health Initiative) data did not prompt any changes to tibolone's SPC regarding the risk of stroke,[4] in that the latter seemed to be comparable to that associated with other HRT.

As a result, the European Pharmacovigilance Working Party (PhVWP) has agreed on including the above information in the SPC and in the Information Leaflet of medicinal products containing tibolone. The text to be included in those documents can be found at:

http://www.hma.eu/222.html

Margarida Guimarães

References

[1] Renoux C, Dell'Aniello S, Suissa S. Hormone replacement therapy and the risk of venous thromboembolism: a population-based study. J Thromb Haemost 2010; 8: 979–86.

[2] de Vries C.S., Bromley S.E., Farmer R.D.T. Myocardial infarction risk and hormone replacement: Differences between products. Maturitas 53 (2006) 343–350.

[3] Million Women Study Collaborators. Breast cancer and hormone-replacement therapy in the Million Women Study. Lancet 2003; 362: 419–27.

[4] Rossouw, JE, Prentice RL, Manson JE, Wu LL, Barad D, Barnabei VM, et al. Postmenopausal Hormone Therapy and Risk of Cardiovascular Disease by Age and Years Since Menopause. JAMA 2007;297:1465-1477.

IV Route Special precautions

In order to minimise adverse effects, health professionals should be aware of the IV prescription/administration parameters given in the products' SPCs, namely **length of time**, **rate** and **concentration**. Whenever the upper limits of administration rate and/or concentration are used, one should bear in mind that any ADRs that may occur may be of greater severity/seriousness. Emergency life support facilities should therefore be available.

The National Pharmacovigilance System has received reports of serious ADRs which are possibly related to the way intravenous medicines were given, namely in short periods of time and/or in high doses.

Data on mode of administration (strength, duration, rate) are especially relevant when an ADR to an IV drug is suspected. Analysing such parameters can be necessary to better inform health professionals in such a way that risks from the use of IV medicines may be minimised.

Certain serious dose-dependent reactions, such as profound hypotension or dyspnoea, can be mistaken for allergic manifestations. This can be of particular relevance, for instance, in the case of IV regimes including antineoplastic agents (e.g., docetaxel, oxaliplatina, paclitaxel, etc) or drugs such as metamizole. The SPC sections on Mode of Administration and Special Precautions for Use should be consulted.

It is worth reminding that any data fed into the National Pharmacovigilance System can only be used for pharmacovigilance purposes, and the System ensures that the reporting professional's and the patient's personal details remain confidential.

Fátima Pereira de Bragança

Proton Pump Inhibitors (PPIs)*: Risk of Hip, Wrist and Spine Fractures Risk of Serious Hypomagnesaemia

In July 2010, the European Pharmacovigilance Working Party (PhVWP) initiated the assessment of a potential risk of bone fractures associated with the use of PPIs. According to the literature, several pathophysiological mechanisms can potentially lead to an increased risk of bone fractures on account of the effects of PPIs on calcium, magnesium and vitamin D balance, as well as on parathyroid hormone and through inhibition of the enzyme vacuolar H^+-ATPase, all with repercussion on bone turnover.

Most epidemiological studies have shown a moderate increase in the risk of hip, wrist or spine fracture. Eight of those epidemiological studies, which were run across a range of different populations, have been presented and discussed by the PhVWP. Evidence from those studies and from meta-analyses suggest there is a **moderate increase in bone fractures** with the use of PPIs (10-40%), mainly hip (10-50%) and spine fractures (30-80%). Risk increases with **prolonged use** (over one year) and with **high-dose** treatments.

Regarding the risk of serious hypomagnesaemia, the number of spontaneous post-marketing reports and of cases in the literature supporting an association between PPI therapy and hypomagnesaemia has been rising since 2006, when the first two cases of omeprazole-associated hypomagnesaemia were reported. In 2011, a review of published cases of hypomagnesaemia related to various types of PPI was presented which included twenty-eight cases from between 2006 and July 2010.

In March 2011, following 38 suspected ADRs and 23 cases published, the FDA issued a safety note addressing health professionals and patients on the risk of low blood magnesium levels associated with **prolonged** (over one year) **use** of IBPs. In May 2011, a Eudravigilance database search came up with 163 reports of hypomagnesaemia involving PPIs.

The mechanism through which PPIs can induce hypomagnesaemia is not known but several hypotheses have been put forward. For instance, PPI-induced hypochlorhydria may alter mineral absorption which is dependent on low pH levels.

Following the above evaluations, and bearing in mind the extensive use of PPIs, the PhVWP has recommended that the moderately increased risks of bone fractures and hypomagnesaemia be communicated to physicians and patients through updates of the SPCs and Information Leaflets of every prescription-only, PPI-containing medicinal product. Evidence so far is not sufficiently robust to demonstrate an increase in risk in over-the-counter products, which are authorised in low-dose formulations and for short periods of time only.

The new risks identified will be included in the SPCs as below (also available at the Infarmed site) and the information leaflets will be updated accordingly.

Section 4.4 Warnings and special precautions for use

Proton pump inhibitors, especially if used in high doses and over long durations (>1 year), may modestly increase the risk of hip, wrist and spine fracture, predominantly in the elderly or in presence of other recognised risk factors. Observational studies suggest that proton pump inhibitors may increase the overall risk of fracture by 10–40%. Some of this increase may be due to other risk factors. Patients at risk of osteoporosis should receive care according to current clinical guidelines and they should have an adequate intake of vitamin D and calcium.

Hypomagnesaemia

Severe hypomagnesaemia has been reported in patients treated with PPIs like <active substance> for at least three months, and in most cases for a year. Serious manifestations of hypomagnesaemia such as fatigue, tetany, delirium, convulsions, dizziness and ventricular arrhythmia can occur but they may begin insidiously and be overlooked. In most affected patients, hypomagnesaemia improved after magnesium replacement and discontinuation of the PPI.

For patients expected to be on prolonged treatment or who take PPIs with digoxin or drugs that may cause hypomagnesaemia (e.g., diuretics), health care professionals should consider measuring magnesium levels before starting PPI treatment and periodically during treatment.

Section 4.8 Undesirable effects

Musculoskeletal disorders

Frequency (uncommon): Fracture of the hip, wrist or spine (see section 4.4)

Metabolism and nutritional disorders

Frequency not known: hypomagnesaemia. [See Special warnings and precautions for use (4.4)]

Catarina Fernandes Costa

* Medicinal products containing dexlansoprazole, esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole (alone or in association with other active ingredients)

ADRs in the Literature… Antibiotic-Associated Diarrhoea: can Probiotics be useful?

Probiotics, live microorganisms intended to confer a health benefit when consumed, have been advocated in the prevention and treatment of antibiotic-associated diarrhea, a common adverse effect. Evidence for this has been challenged by an extensive systematic review and meta-analysis. The majority of the more than 82 RCTs that met the study's inclusion criteria used **Lactobacillus**-based interventions alone or in combination with other genera (Bifidobacterium, Saccharomyces, Streptococcus, Enterococcus, and/or Bacillus), but strains were poorly documented. Although the results are heterogeneous, the pooled evidence suggests that probiotics may be associated with a reduction in antibiotic-associated diarrhoea. More research is needed to determine which probiotics are associated with the greatest efficacy and for which patients receiving which specific antibiotics.

Susanne Hempel et al. JAMA. 2012;307(18):1959-1969