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Editor's Notes

The summaries of two studies of general interest conducted by the INFARMED Pharmacovigilance Department Adverse Drug Reactions Sector are included in this issue.

The first paper gives a glimpse into the initially shy but rapidly growing dynamics of ADR reporting by both community and hospital pharmacists. It was presented at the 32nd European Symposium on Clinical Pharmacy (Valencia, October, 2003).

The second paper is a descriptive study on reported adverse reactions to cox-2 inhibitors, and was awarded a prize for best poster presentation in the field of Pharmaceutical Records and Regulations at the National Pharmacists' Congress (Lisbon, November 2003). Although interestingly raising the issue of adverse reaction patterns of COXIBs and of NSAIDs in general, its methodological design does not allow for any assumptions to be made on possible differences in safety profiles. For the sake of example, amongst other sources of bias, one has only to remind oneself that the proportion of reported ADRs to a recently marketed product with potential for widespread use will probably be much higher than that for long established medicines whose well-known ADRs are not surprising anymore, thus tending to be underreported. Keeping up with the literature on the subject is essential for an opinion on this complex subject. Below a few interesting references can be found for an initial approach and reflection:

- *Brune K, Hinz B. Selective cyclooxygenase-2 inhibitors: similarities and differences. Scand J Rheumatol. 2004;33(1):1-6.*
- *Deeks JJ, Smith LA, Bradley MD. Efficacy, tolerability, and upper gastrointestinal safety of celecoxib for treatment of osteoarthritis and rheumatoid arthritis: systematic review of randomised controlled trials. BMJ. 2002 Sep 21;325(7365):619.*
- *Garner S, Fidan D, Frankish R, Judd M, Shea B, Towheed T, Wells G, Tugwell P. Celecoxib for rheumatoid arthritis (Cochrane Review). In: The Cochrane Library, Issue 2, 2004. Chichester, UK: John Wiley & Sons, Ltd*
- *Garner S, Fidan D, Frankish R, Judd M, Towheed T, Wells G, Tugwell P. Rofecoxib for rheumatoid arthritis (Cochrane Review). In: The Cochrane Library, Issue 2, 2004. Chichester, UK: John Wiley & Sons, Ltd.*
- *Simon LS. COX-2 inhibition: an advance or only pharmaceutical "hype"? Arthritis Rheum. 2001 Jun;45(3):209-15.*
- *Watson DJ, Harper SE, Zhao PL, Quan H, Bolognese JA, Simon TJ. Gastrointestinal tolerability of the selective cyclooxygenase-2 (COX-2) inhibitor rofecoxib compared with nonselective COX-1 and COX-2 inhibitors in osteoarthritis. Arch Intern Med. 2000 Oct 23;160(19):2998-3003.*

Finally, the association between pulmonary interstitial disease and leflunomide, as well as between prolonged QT interval and quinolones, are briefly discussed. In both cases, one is dealing with serious but apparently very rare ADRs.

Rui Pombal

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 Authorization
SPC	Summary of the Product's Characteristics

How can I report an adverse reaction?

yellow *(physicians),* **purple** *(pharmacists) or* **white** *(nurses)* **postage paid card**

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Portugal em Acção

Pharmacists and Pharmacovigilance - What Role?

The National Pharmacovigilance System (NPS) was created in 1992. As any other system based on spontaneous reporting of ADRs, it depends on the active contributions from every health professional. The role of pharmacists in this system has been taking on growing relevance, especially since 1997. We characterised the cases of ADRs reported by pharmacists to the NPS between the 1st of January 1997 and the 31st of December 2002.

Within the above mentioned period of time (Fig. 1), there was a significant increase in the number of reports (from only one in 1997 to 144 in 2002), in a cumulative total of **413 individual cases**. They corresponded to **17% of all direct reports from health professionals, and 9% of the total number of cases reported to the NPS**. Female patients predominated in every age group. They corresponded to sixty percent of the total, with a peak in the seventh decade. Serious cases made up for 42% of total (Fig. 2) SOC (System Organ Classes) more frequently involved were: **general disorders** (22%), **gastrointestinal** (19%), and **skin** (15%) (Fig. 3). The groups of medicines with the greater number of reports did overlap with the more frequently prescribed pharmacological groups.

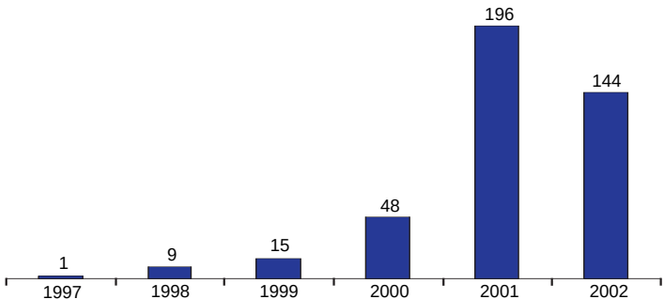


Figure 1. Evolution of the distribution of ADRs reported annually by pharmacists to the NPS (1997-2002).

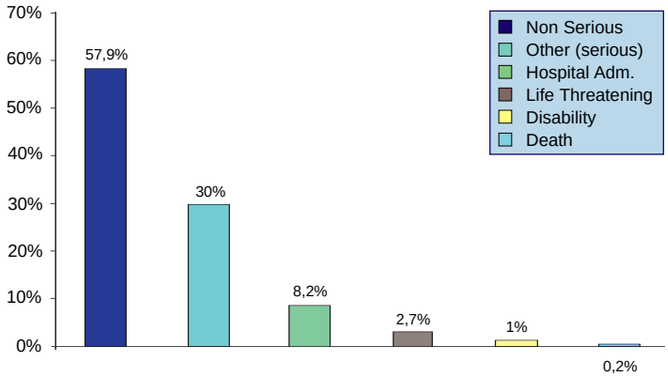


Figure 2. ADR reports from community and hospital pharmacists (1997-2002): seriousness.

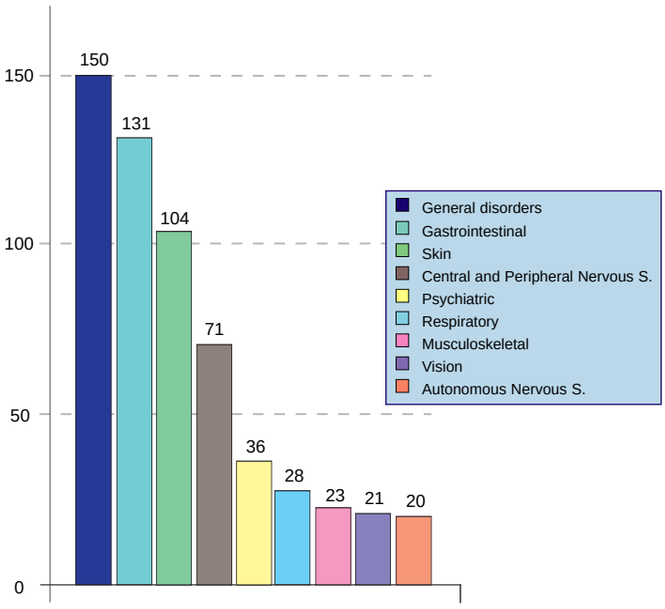


Figure 3. ADR reports from community and hospital pharmacists (1997-2002): distribution by SOC.

These results illustrate ADR underreporting, which is well-known and common worldwide. Considering that community pharmacists dispense 85% of all medicines, a higher number of ADRs from these group of professionals could be expected. Given their proximity to the general population, and considering on the other hand, that hospital pharmacists are part of a multidisciplinary team, there is room for growth in both cases, in spite of their already relevant overall role in pharmacovigilance (Fig. 4).

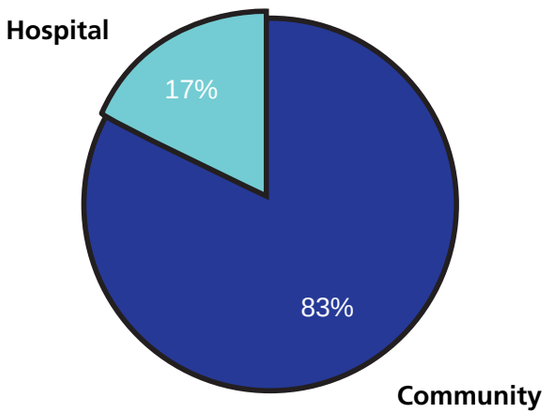


Figure 4. ADR reports from community and hospital pharmacists (1997-2002).

It is necessary and urgent that the institutions in charge of pharmacovigilance motivate pharmacists for ADR reporting, namely by investing in specific training.

Susana Prisca, Ana Araújo, Fátima Bragança, Luís Pinheiro, Regina Carmona

Quinolone Associated Cardiotoxicity

In October 1999, grepafloxacin was withdrawn from the market by its MA holder following reports of fatal cases of serious cardiac rhythm disorders. Grepafloxacin seemed to cause **QT interval prolongation** by blocking cardiac K^+ channels. Also for more recent quinolones, cases of prolonged QT interval and cardiac arrhythmia have been reported. The European Pharmacovigilance Working Party has agreed on the following changes to the SPCs of quinolones:

- **CIPROFLOXACIN**

No text to be included in the SPC.

- **LEVOFLOXACIN**

Section 4.8 (under cardiovascular effects)
Very rarely: QT interval prolongation (see section 4.9)
Section 4.9
According to toxicity studies in animals, or to clinical pharmacology studies with supratherapeutic doses, the most important expected signs following an acute overdose with levofloxacin tablets are central nervous system symptoms such as delirium, dizziness, loss of consciousness and seizures, prolonged QT interval, as well as gastrointestinal reactions such as nausea and mucosal erosions. In case of overdose, symptomatic treatment is indicated, together with ECG monitoring, due to the possible occurrence of QT interval prolongation. Antacids for gastric mucosal protection may be administered. Haemodialysis, including peritoneal dialysis and CAPD, are not effective for the removal of levofloxacin from the body. There is no specific antidote.

- **MOXIFLOXACIN, SPARFLOXACIN**

Warning or contraindication in patients with risk factors such as congenital QT syndrome, hypokalaemia, or taking medications which may prolong the QT interval.

- **NORFLOXACIN**

Section 4.8 (under cardiovascular effects)
Very rarely: QT interval prolongation.

- **OFLOXACIN**

No text to be included in the SPC.

There is currently no evidence of increased risk of QT interval prolongation for either **enoxacin**, **fleroxacin**, **perfloxacin,** or **rufloxacin**.

Adverse Reactions to Selective COX-2 Inhibitors Reported to the National Pharmacovigilance System

ADR reports are extremely relevant for the definition of the safety profile of medicines, especially for the more recent drugs, given the natural limitations of sampling in pre-marketing clinical trials. Characterising ADRs ascribed to selective cox-2 inhibitors (COXIBs) is also relevant due to their being part of the broad group of non-steroidal anti-inflammatory drugs (NSAIDs), some of the most extensively used medicines worldwide. We characterised the ADR reports to COXIBs, and compared them to the total of ADRs to NSAIDs reported to the National Pharmacovigilance System (NPS) between January 1993 and December 2002 (the cases reported from clinical trials were excluded).

The total number of reports of **COXIB ADRs** was **155**. The number of cases for celecoxib (52%) was similar to that for rofecoxib (48%). Most reports (81%) were sent in directly by health professionals, and 19% through the MA holders. Reports concerning COXIBs accounted for **39%** of the total 401 reports **of ADRs to NSAIDs**. The latter corresponded to around 11% of the total number of reports received by the NPS within that period of time (Fig. 1). Reports concerning either COXIBs specifically or NSAIDs in general peaked in 2001. This was however, a year of high overall ADR reporting to the NPS, during which a great number of pharmacovigilance training sessions took place. It was also the year that followed the first year of COXIBs in the market.

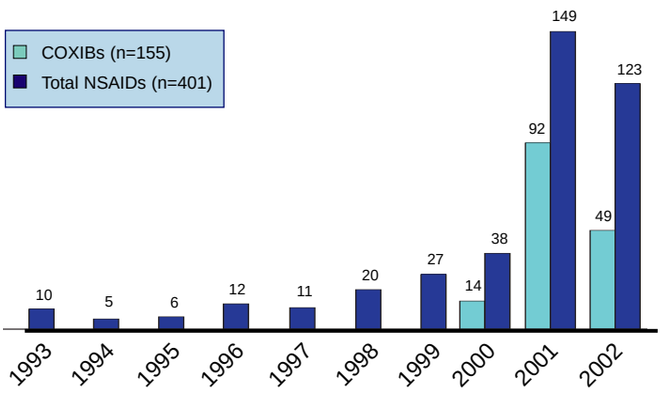


Figure 1. Annual number of reports of ADRs to COXIBs and NSAID total.

Females accounted for the majority of cases in all age groups (74% for COXIBs, and 72% for other NSAIDs). Males are represented in all age groups as well for other NSAIDs, but for COXIBs reports in this gender were only received concerning patients 30 years or older.

Serious cases of ADRs to COXIBs (55%) and NSAIDs (59%) prompted **hospital admission** in **31% and 37%** of cases, respectively.

The System Organ Classes (SOC) **most commonly involved** in association with COXIBs and NSAIDs concerned: the body as a whole, gastrointestinal, skin, central and peripheral nervous system, cardiovascular, vascular, respiratory, urinary, liver

and billiary, platelets and coagulation (Fig. 2). For the gastrointestinal SOC, the most prevalent ADR was **abdominal pain**, whereas **rashes and oedema** were the most prevalent under the skin and whole body SOC.

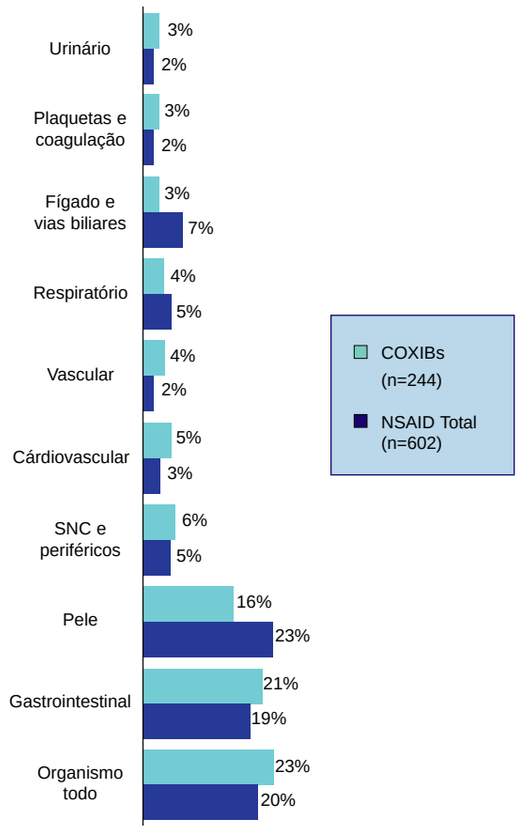


Figure 2. Distribution of ADRs to COXIBs and other NSAIDs by SOC (1993-2002). More than one SOC described may correspond to each report.

In summary, COXIB cases seem to be relevant within the overall context of ADRs to NSAIDs. These results might suggest some similarity between ADRs to COXIBs and to other NSAIDs, in terms of severity, need for hospital admission and most frequently involved SOC, namely allergic and gastrointestinal reactions.

Corresponding to an increased number of reports, the reporting rate for the years of 2001 and 2002 was about 130, still below the desirable ratio of 250 reports per 10^6 reports per year. Pharmacovigilance systems are crucial for the safety evaluation of medicines. Every time a health professional reports an ADR, he or she is making an active contribution towards safer use of medicines.

Fátima Bragança, Susana Prisca, Ana Araújo, Luís Pinheiro, Regina Carmona

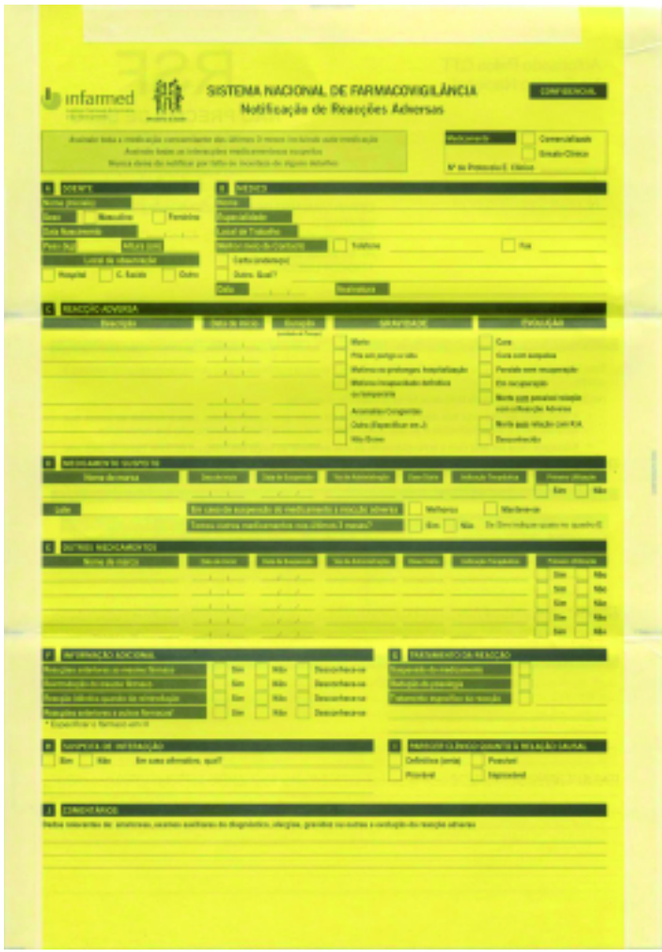
Leflunomide an Pulmonary Interstitial Disease

Arava™ (leflunomide) is indicated for the treatment of adult patients with active rheumatoid arthritis as a disease-modifying antirheumatic drug (DMARD). January last, the Japanese branch of the MA holder gave a set of new precautions exclusively for Japan, following detection of serious respiratory reactions (pulmonary interstitial disease).

In Portugal, as well as all over Europe, Arava™ was granted MA in 1999. Since then, no respiratory ADR associated to it has been reported to the National Pharmacovigilance System.
Pulmonary interstitial disease is a well-known adverse reaction to leflunomide which is mentioned in the SPC* as a very rare undesirable effect (0.01% of patients, or less). However, given those recent cases in Japan, INFARMED, in articulation with all the other European medicines agencies, has been following up on this safety issue very closely.

***The SPC can be accessed at:**
http://www.emea.eu.int/humandocs/Humans/EPAR/Arava/Arava.htm

Online details (Portuguese):
http://www.infarmed.pt/pt/noticias_eventos/noticias/nt_28_01_2004_esclarecimento.html



ADR Report Form (Physicians)