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From the Editor

The National Pharmacovigilance System has come a long way in its development, with an ADR reporting rate per million inhabitants that is more and more approaching the target, and with new challenges on the horizon. The article from the Northern Regional Pharmacovigilance Unit provides an interesting example of how communication tools made available on the internet can be put to relevant use within the System.

The ADR reporting rate facts and figures mirror, up to a certain extent, how mature the System has already become, as well as how much deeper health professionals have grown involved with it. However, it is equally important that health professionals bear in mind report quality and relevance objectives, especially regarding serious and unexpected reactions.

Fluoroquinolones QT Interval Prolongation

The European Pharmacovigilance Working Party at EMA has concluded an assessment on the risk of QT interval prolongation associated with the use of fluoroquinolones. It has been agreed that information in SPCs should be updated. One of the main conclusions is that not all fluoroquinolones seem to have the same potential QT interval prolongation risk. Stratification into **three risk categories** has therefore been proposed. These categories are presented below together with a **summary** of the changes to be introduced in the corresponding SPC sections.

1. POTENTIAL RISK OF INDUCTION OF QT INTERVAL PROLONGATION sparfloxacin, gemifloxacin, grepafloxacin, and moxifloxacin

SPC section 4.3 – contraindications
Both in preclinical investigations and in humans, changes in cardiac electrophysiology in the form of QT prolongation have been observed.

Contraindications:
- congenital or documented acquired QT prolongation
- electrolyte disturbances, particularly uncorrected hypokalaemia
- clinically relevant bradycardia
- clinically relevant heart failure with reduced left ventricular ejection fraction
- previous history of symptomatic arrhythmias
- concurrent use with other drugs that prolong the QT interval

SPC section 4.4 – special warnings and precautions for use (ORAL FORMULATIONS)
In this section quantitative data on the magnitude (in milliseconds) of QT prolongation are given.

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

OR

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

Precautions:
- As **women** tend to have a longer baseline QTc interval compared with men, they may be more sensitive to QTc-prolonging medications.
- **Elderly** patients may also be more susceptible.
- Medications that can **reduce potassium levels** should be used with caution.
- Patients with ongoing **proarrhythmic** conditions (especially women and elderly patients), such as acute myocardial ischemia or QT prolongation. This may lead to an increased risk for ventricular arrhythmias (including torsades de pointes) and cardiac arrest. The magnitude of QT prolongation may increase with increasing concentrations of the drug. Therefore, the recommended dose should not be exceeded.
- If **signs of cardiac arrhythmia** occur during treatment, it should be stopped and an ECG performed.

Additional specific precautions for **IV formulations of moxifloxacin:**
- The **duration of infusion** should not be less than the recommended 60 minutes and the intravenous **dose** of 400 mg once a day should not be exceeded.
- Treatment should be stopped if signs or symptoms that may be associated with **cardiac arrhythmia** occur, with or without ECG findings.
- Caution should be exerted in patients who are taking medications associated with clinically significant **bradycardia**.

SPC section 4.5 – interaction with other medicinal products and other forms of interaction
An additive effect with other medicinal products that may prolong the QT interval cannot be excluded, which might lead to an increased risk of ventricular arrhythmias, including torsades de pointes.

Co-administration of the following is contraindicated:
- anti-arrhythmics class IA (e.g. quinidine, hydroquinidine, disopyramide)
- anti-arrhythmics class III (e.g. amiodarone, sotalol, dofetilide, ibutilide) ▶

INDEX CARD | **Director:** Alexandra Pêgo **Editor:** Rui Pombal **Contributors:** Ana Araújo, Cristina Mousinho, Cristina Rocha, Fátima Bragança, João Ribeiro Silva, Joana Oliveira, Luís Pinheiro, Magda Pedro, Margarida Guimarães, Pedro Marques Silva. **Publishing Assistant:** Inocência Pinto. **Advisory Board:** INFARMED, I.P. Executive Board; Medicines Evaluation Committee. **Publisher:** INFARMED - National Authority of Medicines and Health Produts, I.P., Parque de Saúde de Lisboa, Av. Brasil, N.º 53, 1749-004 Lisboa, Tel. 217 987 100, Fax. 217 987 316, E-mail: infarmed@infarmed.pt **Design and Prodution:** nsolutions - design e imagem, lda. **Printing:** Peres-Soctip, S.A. **Legal Deposit:** 115 099/97 **ISSN**: 0873-7118 **Print Run:** 49.000 (Portuguese)

- antipsychotics (e.g. phenothiazines, pimozide, sertindole, haloperidol, sultopride)
- tricyclic antidepressive agents
- certain antimicrobial agents (sparfloxacin, erythromycin IV, pentamidine, antimalarials particularly halofantrine)
- certain antihistaminics (terfenadine, astemizole, mizolastine)
- others (cisapride, vincamine IV, bepridil, diphemanil).

SPC section 4.8 – undesirable effects (ORAL FORMULATIONS)
In the "cardiac and vascular disorders" subsection frequency of the following will be stated depending on the results of clinical trials: QT interval prolongation, including in patients with hypokalaemia, ventricular tachyarrhythmia, torsades de pointes, non-specified arrhythmia, syncope, and cardiac arrest.

SPC section 4.9 – overdose
In the event of **overdose**, symptomatic treatment should be implemented. ECG monitoring should be undertaken, because of the possibility of QT interval prolongation.

2. LOW POTENTIAL RISK OF INDUCTION OF QT INTERVAL PROLONGATION
ciprofloxacin, levofloxacin, norfloxacin, and ofloxacin

SPC section 4.4 – special warnings and precautions for use and SPC section 4.5 – interaction with other medicinal products and other forms of interaction

Precaution in patients with risk factors known to be associated with QT prolongation such as:
- congenital long QT syndrome
- concurrent use of medicines known to prolong the QT interval (e.g., class I and III antiarrhythmics, tricyclic antidepressants, macrolides, antipsychotic agents)
- uncorrected electrolyte disturbances (e.g., hypokalaemia, hypomagnesaemia)
- heart disease (e.g., cardiac failure, myocardial infarction, bradycardia)
- the elderly

SPC section 4.8 – undesirable effects
Frequency unknown: **ventricular arrhythmia and torsades de pointes** (predominantly reported in patients with risk factors for QT prolongation), **ECG showing QT interval prolongation**.

SPC section 4.9 – overdose: See first category above.

3. VERY LOW POTENTIAL RISK OR INSUFFICIENT DATA TO ASSESS QT INTERVAL PROLONGATION POTENTIAL
enoxacin, lomefloxacin, pefloxacin, prulifloxacin, and rufloxacin

SPC section 4.4 – special warnings and precautions for use
It is stated that other fluoroquinolones have been associated with QT interval prolongation.

SPC section 4.8 – undesirable effects
Frequency of adverse cardiac effects indicated here, depending on cases reported.

Joana Oliveira

ADR Reports in 2010

The number of ADR reports received by the Portuguese National Pharmacovigilance System has been **growing** since it was rolled out in June 1992. Two reporting peaks occurred in the meantime; one in the year 2001 when the regional pharmacovigilance units first started operating, another in 2004, the year a great number of training sessions took place within the scope of a study on reporting motivation factors (Figure 1). In total, from the System's launch until the end of 2010, about 18,200 valid ADR reports have been recorded.

In 2010, 2,143 reports were received, which means the reporting rate in Portugal is still relatively low. However, the evolution seen in the past few years and the current rate of **210 reports/million inhabitants/year** suggest that we are probably on the right track to reach the "ideal" rate of 250-300 reports/million inhabitants/year.

The System's data from 2010 presented here describe the following aspects: reporting channels (direct or indirect) used, reporting professional groups, geographical area whence came the reported cases, and origin and seriousness of ADRs received. Brief comparisons are made with the years 2009 and 2001 (when the regional units started).

The **reporting channels** most used by health professionals in the 2001, 2009 and 2010 samples (Figure 2) were direct sending of reports to INFARMED or to the regional units by post or, more recently, through online reports (the cases of the Northern, Southern and Central Portugal regional units).

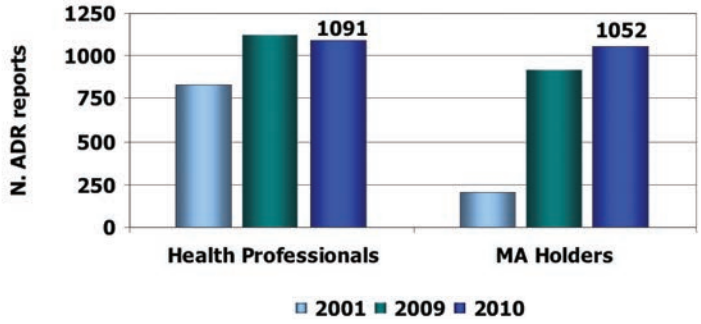

Figure 2. Channels used to report ADRs in 2001, 2009, and 2010.

In 2010, 51% of reports were sent directly to INFARMED, while the remainder reached the agency through the Marketing Authorisation (MA) Holders who had received reports from cases observed by health professionals in their daily practice. Use of indirect channels has been on the increase from 20% in 2001, to 45% in 2009, and up to 49% in 2010. MA Holders are currently sending in their cases electronically (XML files) as prescribed by European guidelines. Still, approximately 2% of those reports were sent into the National Pharmacovigilance System by the old method which required the cases to be entered manually.

Compared to 2009, there was a reversal in relative numbers concerning the professional group which reported the most cases (Figure 3); the number of reports received from physicians increased whereas those from pharmacists and nurses decreased. **Physicians** accounted for the greater bulk of ADR reports (**44% of the total**), followed by pharmacists and nurses.

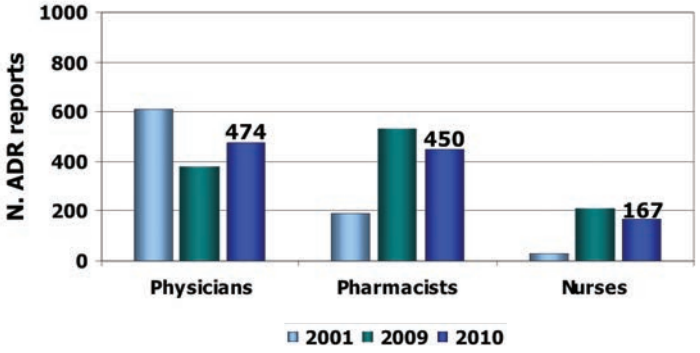

Figure 3. ADR report distribution by health professional type - 2001, 2009, and 2010.

In geographical terms (Figure 4) in 2010, **Northern** Portugal sent in the most cases to the National System (**34%**), followed by the Lisbon and Tagus Valley region, Central Portugal, and the Southern (Alentejo and Algarve) regions. The archipelagos of Madeira and of the Azores accounted for 5% of the nationwide total.

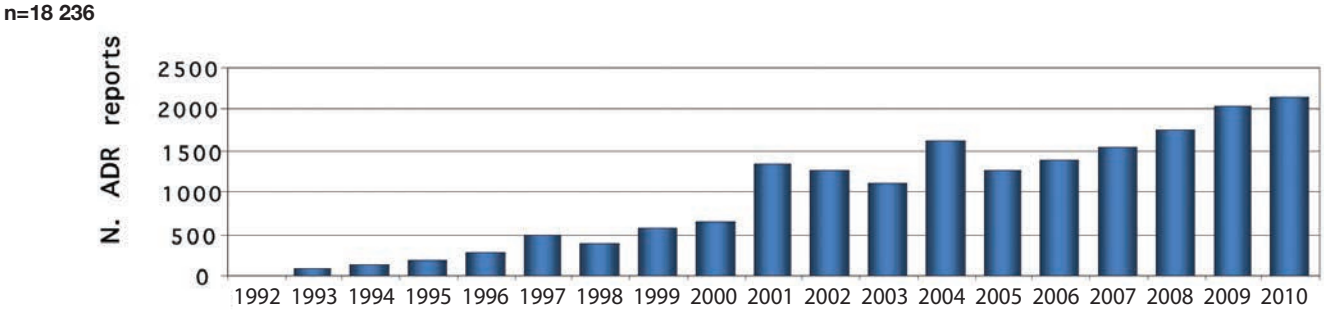

Figure 1. Evolution of the number of ADR reports within the National Pharmacovigilance System.

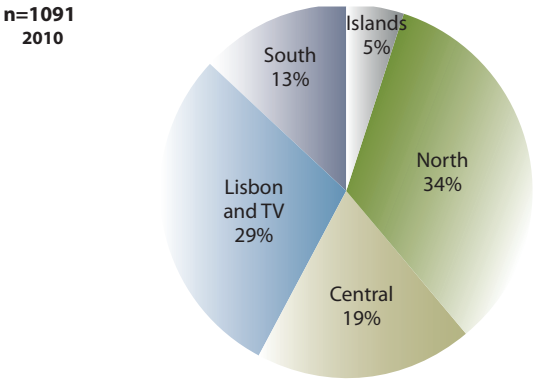

Figure 4. Geographical distribution of ADR reports in 2010.

As for seriousness (Figure 5), the National System received **75%** (1616) of **serious cases** in 2010: 63% of which were received indirectly through MA Holders, 21% directly from physicians, 12% from pharmacists, and 4% from nurses (serious reactions to vaccines). In the preceding year (2009), pharmacists had reported the same proportion of serious cases as physicians (17%). MA Holders communicated to INFARMED in expedited form (maximum 15 day delay) their serious cases of ADRs, as well as cases of lack of efficacy of vaccines, contraceptives, anaesthetics, and other life-saving medicines, according to European guidelines.

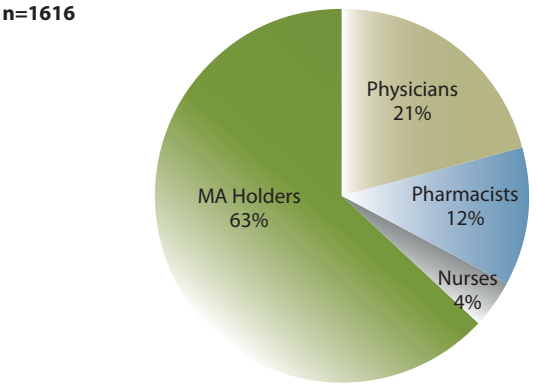

Figure 5. Distribution of serious cases reported by type of originator in 2010.

Most reports entered had all the **minimum data required** for initial validation (contact details of report originator, suspected medicine, suspected adverse reaction, and patient's demographic data such as sex and age). Nevertheless, requests for further data deemed necessary for case analysis and causality assessment frequently prompted **additional contacts** with the reporting professionals. In any case, the National Pharmacovigilance System ensures that data relating to both the patient and the reporting professional are kept confidential.

In summary, 2,143 ADR reports were received in 2010, which corresponds to a growing but still relatively low annual reporting rate of 210 reports per million inhabitants. Since it first started, the National Pharmacovigilance System has cumulatively received a total of approximately 18,200 reports. Most of these (51%) were sent in directly, i.e. by health professionals who reported to the regional pharmacovigilance units or to the agency itself. An almost equal proportion of reports were received indirectly via MA Holders. Physicians were the professional group who reported the most cases. The majority of the reports came from Northern Portugal. In relative terms, the islands, namely Madeira, had a notorious contribution. Of all serious cases received, 63% were sent in via MA Holders and 21% directly by physicians.

Methodological aspects prevent us from completely knowing the safety profile of a medicine before it reaches the market. Data entered in the System from health professionals' daily practice may turn out to be crucial for the continuing risk-benefit assessment of any given medication. Some adverse reactions are of such rarity that they can only be detected after about 30,000 people have been exposed to the drug. Should they be serious, once detected, measures may have to be put in place that can go as far as market withdrawal, depending on existing alternatives and type of ADR, among other factors. Several regulatory measures implemented in the past have resulted from the analysis and assessment of ADR reports.

On a different note, the SPC is an official document which addresses health professionals and contains structured, up-to-date information on safety aspects. It is an extremely useful tool which is only one click away at INFARMED's website (INFOMED page). Professionals who stay alert and informed and report ADRs, cooperate with the National Pharmacovigilance System in its central role to protect the health of citizens. ADR reporting is a paramount activity to that end.

Fátima Pereira de Bragança

Hyperlinks to ADR reporting forms

Aiming to promote online reporting of ADRs, the **Northern** Regional Pharmacovigilance Unit (UFN), in cooperation with the Porto University Medical School Biostatistics and Medical Informatics Department, decided to set up an online tool by using **hyperlinks** in the **electronic clinical records** already existing in the region's network of **hospitals**. The project started off in 2008 and was presented to eighteen hospitals in the region. Of these, thirteen (72%) agreed to participate, some of which by inserting the hyperlink in the software applications used by their health professionals (in wards, consulting rooms, casualty departments, and hospital pharmacies), others by lodging it in the desktops of the professionals' personal computers.

The number of daily visits to the UFN pharmacovigilance unit website increased significantly after the hyperlinks were set up ($p<0.001$). In fact, the median number of **visits per day** to the UFN site went up from ten to 27. Moreover, the **number of ADR reports** submitted through our online form also **increased**. Whereas in 2007 the unit received a median of two monthly reports via the internet form, once the hyperlink had gone live that figure doubled to four in 2008, then eight in 2009 and up to eleven in 2010.

This phase of the project seems to suggest that including direct hyperlinks in the online ADR reporting forms may completely change the health professionals' electronic reporting behaviour, as well as their browsing behaviour in specifically targeted websites. Although the overall total number of ADR reports has not yet increased, health professionals are probably now better informed about spontaneous ADR reporting, since the median number of daily visits to the UFN website (which includes vast amounts of information on pharmacovigilance and adverse reactions) has increased three-fold after inclusion of the hyperlinks. Additionally, there was an increase in the number of reports received online.

The upcoming phases of this project include **information** initiatives addressing health professionals who work in **hospitals** where our tool is already active. At a later stage the scope of the project is to be broadened to include the **health centres** of Northern Portugal.

Inês Ribeiro Vaz (Northern Portugal Regional Pharmacovigilance Unit)

Ethinylestradiol + Drospirenone-containing Oral Contraceptives Risk of Venous Thromboembolism

New epidemiological studies have shown that the **risk** of venous thromboembolism for drospirenone-containing combined oral contraceptives (COCs) is **higher** than for **levonorgestrel-containing COCs (so-called second generation COCs)** and may be **similar** to the risk for **desogestrel/gestodene-containing COCs (so-called third generation COCs)**.

Since the introduction of combined oral contraceptives in 1961, venous thromboembolism (VTE) has been a well-known but **rare** adverse event. VTE has been reported with the use of all combined oral contraceptives (COCs; combination of the two hormone types oestrogen and progestogen), including those containing ethinylestradiol + drospirenone.

Of 100,000 women who are not using a COC and are not pregnant, about 5 to 10 may have a VTE in one year. The corresponding figures for women taking COCs range from about 20 cases per 100,000 women in one year of use for levonorgestrel-containing COCs to 40 cases per 100,000 women in one year of use for desogestrel/gestodene-containing COCs. On the other hand, of 100,000 women who are pregnant around 60 may have a VTE.

Drospirenone-containing COCs have been authorised in the EU since 2000, and include Aliane®, Palandra®, Yasmin®, and Yasminelle®. The risk of VTE has been continuously monitored since approval. Product information was last updated in April 2010 to reflect data from two epidemiological studies on the risk of VTE.[1,2]

The PhVWP agreed to review all available data including recent publications[3,4] and information on additional studies regarding the risk of VTE associated with drospirenone-containing COCs[1-7]. The results from the studies reviewed have shown that drospirenone-containing COCs are associated with a higher risk of VTE than levonorgestrel-containing COCs, whereas their risk may be similar to that of desogestrel/gestodene-containing COCs. This PhVWP ▶

assessment has maintained the conclusion that the **risk of VTE** with **any COC** is **very small**.

The PhVWP recommended that the product information for all drospirenone-containing COCs should be updated to reflect these conclusions. The patient leaflet already contains clear information on symptoms of VTE. There is no reason for women to stop taking drospirenone-containing COCs, such as Yasmin®, or any other COC on the basis of this review.

Adapated from PhVWP May 2011, by Margarida Guimarães

References

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2. *van Hylckama Vlieg A et al. The venous thrombotic risk of oral contraceptives, effects of oestrogen dose and progestagen type: results of the MEGA case-control study. Br Med J. 2009; 339:b2921.*
3. *Jick SS, Hernandez RK. Risk of non-fatal venous thromboembolism in women using oral contraceptives containing drospirenone compared with women using oral contraceptives containing levonorgestrel: case-control study using United States claims data. Br Med J. 2011; 342: d2151.*
4. *Parkin L et al. Risk of venous thromboembolism in users of oral contraceptives containing drospirenone or levonorgestrel: nested case-control study based on UK General Practice Research Database. Br Med J. 2011; 342: d2139.*
5. *Seeger JD et al. Risk of thromboembolism in women taking ethinylestradiol/drospirenone and other oral contraceptives. Obstet Gynecol. 2007; 110: 587-593.*
6. *Dinger JC et al. The safety of a drospirenone-containing oral contraceptive: final results from the European Active Surveillance Study on oral contraceptives based on 142,475 women-years of observation. Contraception. 2007; 75: 344-354.*
7. *Dinger J et al. Risk of venous thromboembolism and the use of dienogest- and drospirenone-containing oral contraceptives: results from a German case-control study. J Fam Plann Reprod Health Care. 2010; 36: 123-129.*

ADRs in the Literature…

Adverse reactions of herbal products for weight loss

The aim of this review was to describe suspected adverse reactions associated with herbal products used for weight control from data collected by the Italian National Institute of Health. Women were involved in 85% of the reports. The majority of weight-loss products (at least 78%) involved contained a **large number of components** (greater than 9). The medicinal herbs most frequently represented, alone or in association, were: **Citrus spp.** (28%), **Fucus spp.** (20%), **green tea** (15%), **Garcinia cambogia** (11%), and **Hoodia spp.** (9%).

The reactions affected mainly the cardiovascular system, the skin, the digestive system, including the liver, and the central nervous system. A large proportion of reactions were serious. Three cases, in which the patients presented serious anticholinergic symptoms, were related to the consumption of different herbal products prepared with the same batch of Coleus forskohlii that had been contaminated by tropane alkaloids. In **52%** of suspected adverse reactions patients were **also taking other herbs and/or pharmaceutical products** (fluoxetine, metformin, and levothyroxine).

Considering the risk/benefit ratio, the authors remind us that consumers should use caution when using these products.

Vitalone A et al. Suspected adverse reactions associated with herbal products used for weight loss: a case series reported to the Italian National Institute of Health. Eur J Clin Pharmacol (2011) 67:215–224.

ADRs in the Literature…

Paracetamol taken for more than two days may be associated with INR prolongation in patients on warfarin

In this prospective, randomised, parallel, placebo-controlled study, the authors investigated whether paracetamol, given at **2 g/day** and **3 g/day** might potentiate the anticoagulant effect of warfarin. Forty-five patients on stable warfarin therapy were enrolled. The mean maximal **INR increase** was **0.70±0.49** and **0.67±0.62** in patients receiving paracetamol at 2 g/ day and 3 g/day, respectively. The INR increase became **significant on day 3**.

Qian Z et al. Interaction between acetaminophen and warfarin in adults receiving long-term oral anticoagulants: a randomized controlled trial. Eur J Clin Pharmacol (2011) 67:309–314.

ADRs in the Literature…

Haemorrhagic risk associated with aspirin: dose is of the essence

In short-term trials, aspirin is associated with gastrointestinal bleeding. However, the effect of dose and duration of aspirin use on risk remains unclear. In this prospective study of 87,680 women enrolled in the Nurses' Health Study the authors examined the relative risk of major gastrointestinal bleeding during a 24-year follow-up. Regular aspirin use is associated with gastrointestinal bleeding. Risk seems more strongly related to dose than duration of aspirin use. The authors conclude that efforts to minimize adverse effects of aspirin therapy should therefore emphasize using the lowest effective dose among both short- and long-term users.

Huang ES et al. Long-term use of aspirin and the risk of gastrointestinal bleeding. The American Journal of Medicine (2011) 124, 426-433

ADRs in the Literature…

HLA-A*3101 allele: risk factor for carbamazepine-induced hypersensitivity reactions

Carbamazepine causes various forms of hypersensitivity reactions, ranging from maculopapular exanthema to severe blistering reactions. The HLA-B*1502 allele has been shown to be strongly correlated with carbamazepine-induced Stevens–Johnson syndrome and toxic epidermal necrolysis (SJS–TEN) in the Han Chinese and other Asian populations but not in European populations. The authors performed a genomewide association study of samples obtained from subjects with carbamazepine-induced hypersensitivity syndrome or maculopapular exanthema, and 3987 control subjects, all of European descent.

The HLA-A*3101 allele, which has a prevalence of 2 to 5% in Northern European populations, was significantly associated with the hypersensitivity syndrome. Follow-up genotyping confirmed this variant as a risk factor for the hypersensitivity syndrome, maculopapular exanthema and SJS–TEN. The presence of the allele increased the risk from 5.0% to 26.0%, whereas its absence reduced the risk from 5.0% to 3.8%.

*McCormack M et al. HLA-A*3101 and Carbamazepine-Induced Hypersensitivity Reactions in Europeans. N Engl J Med 2011; 364:1134-1143.*

Interactions to keep in mind!

Bipolar Patients*

Risk of:

Lithium overdose (by interfering with renal excretion of lithium)

- Non-steroidal anti-inflammatory agents (NSAIDs)
- Diuretics
- Angiotensin converting enzyme (ACE) inhibitors, and angiotensin II antagonists (sartans)

Reduction of plasma lithium concentration

- Sodium intake

Risk of undesirable neuropsychiatric effects with lithium + neuroleptic associations.

** Based on: la revue Prescrire*