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Direct access of healthcare professionals to Information on adverse drug reactions

Quick Read

The EudraVigilance database contains suspected adverse reaction reports from the European Economic Area. The European Medicines Agency has defined an access policy which not only ensures transparency, but also confidentiality and personal data protection. There already is an online tool at http://www.adrreports.eu/pt/index.html which gives access to ADR web reports searchable by trademark name or by active ingredient name. The World Health Organization (WHO) also provides a tool – VigiAccess – which allows for searching and obtaining statistical data on suspected adverse reactions to several medicinal products. All these data should be interpreted with caution and appropriately put into context together with other safety data currently available.

Reporting suspected adverse drug reactions (ADRs) either directly to the national medicines regulatory authority (INFARMED I.P. in the case of Portugal), or via the medicinal product's Marketing Authorization (MA) Holder (commonly known as the "pharmaceutical company") makes up the basis of both the national and the European pharmacovigilance data systems.

The authorities and the pharmaceutical industry both feed the European database **EudraVigilance** with the ADR reports pertaining to every medicinal product authorized within the European Economic Area (EEA). The benefit-risk ratio of medicines throughout their life cycle can be assessed and their post-marketing safety monitored thanks to that information. All the member states are under the obligation to retransmit their Individual Case Safety Reports (ICSRs) into the European database. Thus, by taking part in their own national pharmacovigilance system, namely by reporting ADRs, Portuguese healthcare professionals are actively contributing towards the international system as well.

The policy of the European Medicines Agency (EMA) for accessing Eudravigilance was reviewed in 2015 and can be consulted in document form at EMA's website (click **here**).

What do they mean?

ADR	Adverse Drug Reaction
EMA	European Medicines Agency
MA	Marketing Authorization
PIL	Patient Information Leaflet
PRAC	Pharmacovigilance Risk Assessment Committee (EMA)
SmPC	Summary of Product Characteristics

INDEX CARD

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Six major groups of system participants are defined together with their levels of access: I) EEA member state regulatory authorities, II) healthcare professionals and public in general, III) MA holders, IV) academia, V) World Health Organization Monitoring Centre (in Uppsala, Sweden), and VI) regulatory authorities from third-party states (e.g., USA, Japan).

This access policy has been set up to provide as much information as possible and is guided by principles of **transparency**, but also of **confidentiality and personal data protection** assurance. Access thus defined has various advantages such as:

- to improve public health through medicinal product safety monitoring;
- to support signal (suspected safety problem) detection;
- to make information available to healthcare professionals and the public in general;
- to make Eudravigilance data available for scientific research.

Already since 2012, EMA has been making available an online tool (in **Portuguese**; in **English**) – the European database of suspected adverse drug reaction reports, which provides access to ADR web reports extracted from Eudravigilance. Searches can be undertaken by using either the product's trademark name or its active ingredient name.

Both healthcare professionals and the public at large can use this web tool to access a limited set of spontaneous ADR report data, as well as guidance on the nature and interpretation of data (e.g., patients are advised not to change their medication without first consulting a healthcare professional).

With this tool one can look up cases for which the reporting person suspected that a medicinal product or an active ingredient was the cause or a specific contributory factor (e.g., drug-drug interaction) for a **serious** side effect. These web reports **do not include** reports from research studies (e.g., clinical trials, non-interventional studies), nor other types of non-spontaneous reports. They do not include therefore reports which, for instance, have been previously and specifically elicited form healthcare professionals.

There is yet another tool made available by the World Health Organization (WHO) for public access to medicinal product safety data, **VigiAccess**, which allows for searches for statistical data on suspected ADRs to various medicines. All the data available here come from VigiBase®, the WHO global ADR database kept by the Uppsala Monitoring Centre (UMC), and originate from ADR reports collected by the regulatory authorities of over 110 countries and for over 100,000 medicines.

It should be noted that **information on presumed ADR cases contained in all these databases should be interpreted with caution**. The **fact that a given adverse effect occurred does not mean that the medicinal product or active ingredient in question has caused that effect, nor does it mean that its use may not be safe**. Robust conclusions regarding the risk-benefit ratio of a specific medicinal product always require a detailed analysis to find out whether a causal relationship between reaction and drug may or may not exist (causality assessment), as well as a scientific assessment also including all other available data, namely from other information sources, such as post-authorization safety studies, clinical trials and toxicological studies.

Vanda Araújo

ADRs in the Literature
QT interval, medicines and risk of arrhythmia

A prolonged QT on the electrocardiogram (ECG) can be associated with ***torsade de pointes***, a potentially fatal cardiac arrhythmia. Although a long QT may rarely be part of a hereditary syndrome, it is more often caused by drugs, especially in the presence of additional risk factors.

The QT interval is measured on the ECG from the start of the QRS complex to the end of the T wave. It corresponds to the period going from the start of depolarization to the end of repolarization of the ventricular myocardium. Its length varies greatly with age, gender, sympathetic tonus and time of day, and increases as heart rate decreases in a ratio that varies from individual to individual. Measuring the QT interval can therefore be a problem and current guidelines tend to recommend mathematical linear regression functions such as the Framingham method:

$$QTc = QT + 0{,}154(1-RR)$$

(QTc = QT corrected for heart rate; RR = interval between successive R waves)

In general, 450 ms for men and 460 ms for women are accepted as the upper limits of normal in adults. The risk of developing torsades de pointes (TdP) and sudden death is related both to QT duration and its increase. Each 10-ms prolongation of QTc is associated with an increased risk of arrhythmia of 5 to 7 percent. In absolute terms, a QTc longer than 500 ms usually indicates high risk.

All the above notwithstanding, many individuals with a long QT never have arrhythmia and some drugs, such as amiodarone, though able to significantly prolong it, are in fact only rarely associated with the occurrence of TdP.

Drugs that may cause QT prolongation

Antiarrhythmic and other cardiac agents
amiodarone, disopyramide, dronedarone, flecainide, rabolazine, sotalol
Antibacterials
macrolides, quinolones
Antifungals
fluconazole, ketoconazole
Antiemetics and GI motility inhibitors
domperidone, granisetron, ondansetron
Antimalarials
chloroquine, quinine
Antihistamines
hydroxizine
Antipsychotics
chlorpromazine, clozapine, droperidol, fluphenazine, haloperidol, olanzapine, pimozide, paliperidone, quetiapine, risperidone
Antidepressants
amitriptyline, citalopram, escitalopram, dosulepine, doxepine, fluoxetine, imipramine, lofepramine
Miscellaneous
methadone, antiretrovirals (e.g., foscarnet), protein kinase inhibitors (e.g., sorafenib, sunitinib)

Risk factors for TdP with QT prolongation

- Female sex, old age
- Electrolyte imbalance (e.g., hypokalaemia)
- Genetic predisposition, ion channel anomalies
- Liver or kidney impairment
- Cardiac factors: baseline long QT, occult long QT syndrome, bradycardia, recent cardioversion with a drug that prolongs the QT interval, underlying cardiopathy (heart failure, left ventricular hypertrophy, myocardial infarction)
- Pharmacological factors: drug interactions from the use of more than one QT-prolonging drug, or a diuretic, or digoxin; rapid intravenous infusion or high concentration of a QT-prolonging drug

Most cases of QT prolongation induction caused by drugs actually occur in the presence of at least one additional risk factor (above), while **70% of cases occur only in the presence of two or more such factors**.

In clinical practice, the authors of this BMJ Drug and Therapeutics Bulletin review recommend that patients at high risk of pharmacological QT prolongation who need a drug with that potential effect and for whom no other alternative is available, should have a **previous baseline** and then a follow-up **ECG** undertaken, especially **when the drug reaches its steady state**. These patients should be advised on alarm signs and symptoms of arrhythmia and on when to seek medical help.

Whenever the QTc reaches **470-500 ms in a man** or **480-500 ms in a woman**, or when **QTc prolongation is 60 ms or more**, the authors propose that the dose be reduced or therapy be discontinued. Should the QTc reach 500 ms, the medication should be stopped, the ECG repeated and specialist opinion sought.

In addition to a preventive attitude in clinical practice, minimizing the risk of arrhythmia with drugs that prolong the QT interval is based on a two-fold approach: screening at the medicinal product development stage and regulation and post-marketing pharmacovigilance. The role of ADR reporting by healthcare professionals is especially relevant for the latter.

BMJ 2016;353:i2732

Educational Materials published on the Infarmed website

Medicinal product (DCI)	Click on the links (in Portuguese)
Aripiprazol Mylan Pharma (aripiprazole)	***Information for physicians*** Guia de questões frequentes para o psiquiatra/pedopsiquiatra prescritor – 1.ª versão ***Information for patients*** Guia para doentes/prestadores de cuidados de saúde – 1.ª versão Published on 31-10-2016
Benepali (etanercept)	***Information for physicians*** Guia de consulta rápida – caneta (com material educacional para o doente) – 1.ª versão Guia de consulta rápida – seringa pré-cheia (com material educacional para o doente) – 1.ª versão Breve formação sobre medidas adicionais de minimização do risco – 1.ª versão Published on 09-11-2016
Flixabi (infliximab)	***Information for physicians and pharmacists*** Guia de informação de segurança – 1.ª versão Folha de triagem do doente – 1.ª versão Calendário de perfusão – 1.ª versão Published on 31-10-2016
Truvada (emtricitabine + tenofovir)	***Information for physicians*** Profilaxia pré-exposição (PrEP) – 1.ª versão Lista de verificação sobre a PrEP – 1.ª versão ***Information for individuals at risk*** Informação importante sobre Truvada para reduzir o risco de contrair a infeção pelo VIH – 1.ª versão Cartão lembrete sobre a PrEP Published on 27-10-2016

Communications to Healthcare Professionals

Medicinal product (DCI)	Click on topic for details (in Portuguese)
Adempas (riociguat)	New contraindication in patients with pulmonary hypertension associated with idiopathic interstitial pneumonia **Erratum:** in its original publication in Boletim issue 3, 2016 (September) this linked to the wrong document. The link is now corrected.. Published on 05-07-2016
Blincyto (blinatumomab)	Risk of pancreatitis Published on 26-09-2016
Revlimid (lenalidomida)	New important recommendation on reactivation and monitoring throughout treatment Published on 26-09-2016

Compiled by Magda Pedro