boletim de FARMACOVIGILÂNCIA

Ministério da Saúde

infarmed
Autoridade Nacional do Medicamento e Produtos de Saúde I.P.

VOLUME 13
NÚMERO 2
2ND QUARTER 2009

Editor's Notes

Is it an interaction??

This Volume of the Boletim highlights issues concerning drug interactions. A new section is now started on drug interactions involving pharmacotherapeutic groups that are characteristically used in certain patient types. *The reminders focus on interactions that are especially relevant on account of their frequency, seriousness, severity and/or specificity. Interaction risks in patients submitted to anti-obesity pharmacological therapies will be the subject of the first of these sections. The French journal Prescrire is the main source for these reminders, namely a special guidance issue to help professionals to better understand, decide and prevent adverse reactions originating from drug interactions.*

DIPS – a causality assessment tool for suspected interactions

To ascribe an adverse reaction to a given medicinal product, i.e. to determine or assess a potential causal nexus, is one of the most complex tasks in ADR report evaluation activities. The process is all the more complex when assessing a potential drug interaction. Looking for objective and reliable tools for drug interaction causality evaluation, several authors have made use of the well-known Naranjo scale. However, the latter was designed to evaluate adverse reactions caused by a single drug, and its role is markedly hampered whenever one tries to extrapolate it to analysing suspected medicinal interactions.

Horn, Hansten and Chan, starting from the Naranjo scale but going a step further, propose a specific tool for this type of causality assessment - the DIPS, Drug Interaction Probability Scale.

This tool consists of 10 questions each with three response options to which a score is given. The final score translates into a qualitative scale expressing the probability of the reaction actually being a drug interaction (see Table overleaf). The score obtained is not absolute, neither can it be extrapolated to other similar cases, but is relevant for determining how likely each individual case of ADR is to have originated from an interaction.

What do they stand for?!

ADR	Adverse Drug Reaction
CHMP	Committee for Medicinal Products for Human Use
EMEA	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
yellow *(physicians)*, **purple** *(pharmacists)* **or white** *(nurses)*

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

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INFARMED, Lisbon
Target audience: physicians, pharmacists, nurses, and students
Further details at:
http://www.infarmed.pt/portal/page/portal/INFARMED/EVENTOS/DETALHE_EVENTO?eventoid=1386269

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INDEX CARD | **Director:** Júlio Carvalhal **Editor:** Rui Pombal **Assistant Editor:** Alexandra Pêgo **Contributors:** Ana Araújo, Cristina Rocha, Fátima Bragança, João Ribeiro Silva, Madalena Arriegas, Magda Pedro, Margarida Guimarães , Pedro Marques Silva. **Publishing Assistant:** Adélia Noronha. **Advisory Board:** Vasco Maria, Luísa Carvalho, Hélder Mota Filipe (INFARMED, I.P. Executive Board); INFARMED, I.P. 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:** Tipografia Peres **Legal Deposit:** 115 099/97 **ISSN**: 0873-7118 **Print Run:** 40.000

DIPS
Drug Interaction Probability Scale

Question	Yes	No	Unknown or Non Applicable
1. Are there previous *credible* reports of this interaction in humans?	+1	-1	0
2. Is the observed interaction consistent with the known interactive properties of precipitant drug?	+1	-1	0
3. Is the observed interaction consistent with the known interactive properties of precipitant drug?	+1	-1	0
4. Is the event consistent with the known or reasonable time course of the interaction (onset and/or offset)?	+1	-1	0
5. Did the interaction remit upon dechallenge of the precipitant drug with no change in the object drug? (if there was no dechallenge, choose *Unknown or Non Applicable* and skip question 6)	+1	-2	0
6. Did the interaction reappear when the precipitant drug was readministered in the presence of continued use of object drug?	+2	-1	0
7. Are there reasonable alternative causes for the event?[a]	-1	+1	0
8. Was the object drug detected in the blood or other fluids in concentrations consistent with the proposed interaction?	+1	0	0
9. Was the drug interaction confirmed by any objective evidence consistent with the effects on the object drug (other than drug concentrations from question 8)?	+1	0	0
10. Was the interaction greater when the precipitant drug dose was increased or less when the precipitant drug dose was decreased?	+1	-1	0

[a] Consider clinical conditions, other interacting drugs, lack of compliance, risk factors (e.g., age, inappropriate doses of object drug). A No answer presumes that enough information was presented so that one would expect any alternative causes to be mentioned. When in doubt, use Unknown or NA designation.

Total Score:

Highly Probable	**>8**
Probable	**5-8**
Possible	**2-4**
Doubtful	**<2**

NB:
Object drug: the one affected by the presence of another drug.
Precipitant drug: the one causing a change on the object drug.

A few notes on the practical use of the DIPS

Question 1

The following are considered *credible* for this purpose:

- prospective studies showing clear evidence supporting the interaction, or

- case reports giving evidence to support the interaction, including cases in which applying the DIPS produces a result of *possible* or higher.

Question 2

The lists of enzyme inducers and inhibitors should be carefully pondered, since in vitro evidence does not always apply to in vivo conditions in straightforward manner.

Question 3

This calls for robust knowledge on the pharmacodynamic and pharmacokynetic characteristics of the object drug. In particular, medicines whose pharmacodynamics is affected by multiple factors may lead to false positive assessment outcomes. In the case of warfarin, for instance, the influence of dietary factors (vitamin K content) can easily be underestimated or altogether overlooked.

Question 4

The time lapse necessary for maximum inhibition to occur can be estimated from the half-life of the precipitant drug, whereas the half-life of the object drug will allow for the time of maximum change of the object drug to be estimated.

Question 5

These data are often unavailable in that both precipitant and object drug are often discontinued when a suspicion of interaction is raised. Neither can the dechallenge effect be evaluated if the doses of both drugs are changed.

Question 6

In those rare cases, usually due to unintentional rechallenge, that these data are available, the robustness of the causal relation obtained ends up being greatly reinforced.

Question 7

In this context, one of the most important limitations to causality assessment is insufficiently exploring alternative explanations for the observed reaction, other than a drug interaction.

Question 8

The answer to this question will often be "Non applicable", since pharmacodynamic interactions do not usually entail changes in the concentrations of the object drug.

Question 9

Changes in physiological (laboratory) parameters may typically be objective evidence of a drug interaction.

Question 10

In those rare cases in which a dose-response relation can be established, the causality nexus is strongly reinforced.

The DIPS may well have significant limitations such as its as yet relatively limited use, the need for data that are often unavailable, as well as the need for relatively in-depth knowledge on both the implicated medicines. This scale however, shows great potential to become an indispensable tool for the evaluation of suspected drug interactions from an individual, case-by-case perspective.

Horn JR, Hansten P, Chan L-N. Proposal for a new tool to evaluate drug interaction cases. Annals Pharmacotherap 2007;41:674-80.
Naranjo CA, Busto U, Seller EM, et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther 1981;30:239-45.

Centre Regional Pharmacovigilance Unit

Pharmacovigilance: the Centre Regional Pharmacovigilance Unit, AIBILI, and the future

1. As the National Pharmacovigilance System Centre Regional Unit **resumes its activity** a new cycle is begun which aims for the development, validation and adaptation of methods to detect adverse events associated with drug exposure.
2. All the scientific output and **experience gained** during its initial four years (2000-2004) indicate and make it a necessity that regional units such as this should be on the way to becoming pharmacoepidemiological research hotbeds able to bring together and potentiate the know-how of health science university hubs such as Coimbra's.
3. **Spontaneous ADR reporting** should be promoted on a continuing basis, provided qualitative and quantitative research and analysis is conducted accordingly.
4. It is anticipated that the paradigm for models of drug funding and co-payment is changing in such a way that post-marketing safety evaluation will take on a crucial role in gauging effectiveness. **New needs** to assess the impact of the use of medicines in contexts like the above make up for additional working opportunities for regional pharmacovigilance units.
5. The **contracting model** established between the regulatory authority (INFARMED) and the regional unit is in practice a form of service outsourcing. Its flexibility may be further explored to expand the national pharmacovigilance system into a much needed nation-wide pharmacoepidemiological network.
6. **Teaching and post-graduate institutions**, especially medical and pharmaceutical schools, can find in the regional unit an additional resource to help them fulfil their missions. Moreover they are thus able to integrate teaching, service and research under the same roof.
7. **Health professionals** working in this Region, thanks to their input through ADR reporting, are indispensable partners in our final and common goal: to optimise patient safety.

Finally, **health policy decision-making**, namely in what concerns the medicinal product environment, should bear in mind that pharmacovigilance is a structural pillar of sustainability for health systems.

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Risk of Atypical Stress Fractures associated with the use of Alendronic Acid

There have been reports of cases of stress fractures of the proximal portion of the femoral diaphysis in patients submitted to **long term treatment** (18 months to 10 years) with alendronic acid.

The European Pharmacovigilance Working Party (PhVWP) has evaluated all data available on biphosphonates and risk of atypical stress fractures, including data from the published literature, pre-clinical studies, clinical trials, and post-marketing reports. It has been concluded that the available data support an association between atypical stress fractures and the long term use of alendronic acid. However, these data **do not suggest** that there is evidence of an increased incidence of atypical stress fractures with **other biphosphonates**. It is unclear whether this lack of evidence for other biphosphonates is due to limited use, to limited long-term data, or to a specific effect of the active substance, alendronic acid. The intense bone regeneration suppression mechanism involved may well be relevant for all biphosphonates, and **a possible class effect cannot be excluded**.

The **SPCs and Information Leaflets are going to be altered** in order to include information on the above risk.

Margarida Guimarães

Metabolic Monitoring in patients treated with Second Generation Antipsychotics

Patients with schizophrenia or other psychiatric illnesses have an increased risk of comorbid physical conditions, including diabetes, complications of diabetes, and cardiovascular disease. The use of antipsychotic medicines (**including second generation drugs such as olanzapine, risperidone, quetiapine, ziprasidone, aripiprazole**) can trigger or worsen these metabolic changes, which should therefore be carefully monitored.

The **Consensus Development Conference on Antipsychotic Drugs and Obesity and Diabetes** (American Diabetes Association, American Psychiatric Association, American Association of Clinical Endocrinologists, and North American Association for the Study of Obesity) reflects a joint statement by a group of specialist physicians involved in the treatment of psychiatric diseases, obesity and diabetes. It aims to make it clear which are the best procedures to follow in order to minimise the risk of metabolic changes caused by therapy with second generation antipsychotics (SGAs).

Monitoring schedule proposed by the guideline

	Baseline	4th week	8th week	12th week	Quarterly	Annually	Every 5 years
Personal/family history	X					X	
Weight (BMI)	X	X	X	X	X		
Abdominal waist	X					X	
Blood pressure	X			X		X	
Fasting plasma glucose	X			X		X	
Fasting lipid profile	X			X			X

Psychiatrists should not hesitate to refer the patient. On the other hand, nutrition and physical activity counselling should be provided for all patients who are overweight or obese, particularly if they are starting treatment with an SGA that is associated with significant weight gain. Referral to a health care professional or programme with expertise in weight management may also be appropriate.

If a patient gains ≥5% of his or her initial weight at any time during therapy, one should consider switching the SGA. In such a situation, the panel recommends cross-titration; abrupt discontinuation should generally be avoided.

For people who develop worsening glycaemia or dyslipidaemia while on antipsychotic therapy, the panel recommends considering switching to an SGA that has not been associated with significant weight gain or diabetes.

drug	Weight gain	Risk of diabetes	Worsening lipid profile
Clozapina	+++	+	+
Olanzapina	+++	+	+
Risperidona	++	D	D
Quetiapina	++	D	D
Aripiprazole*	+/–	–	–
Ziprasidone*	+/–	–	–

+ = increased effect; – = no effect; D = discrepant data
** more recent drugs with limited long-term data*

All patients with diabetes should be referred to a recognised diabetes self-management education program, if available. Referral to a clinician experienced in treating people with diabetes is recommended. Although goals need to be individualised, blood pressure, lipid, and glycaemic **goals** for people with diabetes **apply equally** to those who also have psychiatric disorders.

Interactions to keep in mind
Patients being treated for obesity

Sibutramine

- ◆ metabolised by cytochrome P450 3A4
- Risk of increased dose-dependent adverse effects [cytochrome inhibition] with:
  - amiodarone, diltiazem, verapamil
  - macrolides (except spiramycin)
  - azole antifungals
  - certain antiretrovirals
  - grapefruit juice
- Risk of serotoninergic syndrome [summative effect]
  - MAO inhibitors in general, including the antibiotic linezolide
  - serotonin and noradrenalin reuptake inhibitor antidepressants
  - certain opioids (v.g., pethidine and tramadol)
  - lithium
  - triptans and dihydroergotamine
  - buspirone
- Risk of hypertension
  - corticoids, NSAIDs [summative effect]
  - venlafaxine, duloxetine, bupropion, nasal decongestants, triptans, MAO inhibitors, epoetins, levothyroxine,...
  - chronic alcohol consumption
- Risk of tachycardia
  - alpha and beta-agonists
  - levothyroxine, ...
- Risk of haemorrhage [summative effect]
  - antiplatelet agents, warfarin, ...
- Risk of decreased effect of antiglaucoma drugs [increased intraocular pressure]

Orlistat

- ◆ Little absorbed, eliminated fecally essentially unchanged

Risk of

- pregnancy with oral contraceptives [in case of major diarrhoea]
- vitamins ADEK deficiency [lipid-soluble vitamins]
- haemorrhage with vitamin K antagonists
- reduced effect of antiarrhythmics [decreased absorption]

The following may counter the weight loss effect:

- insulin (antidiabetic sulphonamides and glitazones)
- neuroleptics
- certain antidepressants
- certain antiepileptics (v.g., sodium valproate, gabapentin, pregabalin, levetiracetam, vigabatrin)
- piracetam
- certain anti-H1 antihistamines (v.g., cyproheptadine, pizotifen, ketotifen, phenothiazines)
- corticoids, danazol, raloxifen, tibolone, progesterone, ciproterone, megestrol
- methysergide; cyclosporin;...

Based on: la revue Prescrire

Products for the prevention and treatment of Head Lice Danger of Fire

The Dutch medical device regulatory authority and the MA holder of the medicinal product Piky (available in Portugal) have made it known to INFARMED that, in several European countries, there have been some cases of serious hand and head burns related to the use of topical solutions for the prevention and treatment of human pediculosis. These products contain dimethicone (4%) and cyclomethicone (96%). When in contact with these products hair may be flammable. It is therefore recommended that after these solutions are applied hair should be kept away from sources of ignition, such as cigarettes, matches, lighters, or candles.

ADRs in the literature...

Atypical antipsychotics with typical manifestations

Medline and Embase were reviewed for case reports and systematic reviews. In general, the neuroleptic malignant syndrome seems to have a typical presentation also with atypical antipsychotics, clozapine excepted, which seems to cause fewer extrapyramidal effects such as rigidity and tremor.

Trollor JN, Chen X, Sachdey PS. CNS Drugs;23(6):477-92

What should one report?

Every suspected serious adverse reaction, even if already previously described. Seriousness criteria include:

- causing death
- life threatening
- prompting hospital admission
- prolonging hospital stay
- resulting in persistent or significant incapacity
- suspected congenital anomaly or malformation.

Every suspected adverse reaction which has thus far **not been described** (unknown thus far), even if not serious or severe.

Every suspected **increase in the frequency** of ADRs (both serious and non-serious)