boletim de FARMACOVIGILÂNCIA

Ministério da Saúde

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

VOLUME 14
NUMBER 4
4TH QUARTER 2010

From the Editor

To predict and therefore prevent ADRs with reasonable accuracy is an ideal goal whose complete achievement will probably remain elusive. The good news is it is becoming more and more manageable as our knowledge on the behaviour of medicines in real practice increases, and as pharmacovigilance practices around the world evolve.

One preventive strategy which has gained considerable relevance in later years has been the adaptation of prescription guidelines or privileges to novel safety data. Limiting the use of fibrates to second line therapy is an example, as well as the specific recommendation to prescribe lower doses of saquinavir during the first week of treatment. In-depth knowledge of pharmacodynamic and pharmacogenetic aspects of drug interactions can also be very useful to prevent the use of deleterious drug combinations. This is illustrated by the article on tamoxifen and genetic variants of CYP2D6.

ADRs in children always pose a major challenge to health professionals. Our knowledge in this field now benefits from additional Portuguese National Pharmacovigilance System data from spontaneous ADR reporting encompassing the paediatric age groups.

Fibrates
Second-line therapy

Fibrates have been subjected to an initial Europe-wide assessment process in 2005, on account of limited evidence of their benefit in reducing long term cardiovascular risk. At that time, it was concluded that these drugs still have a role in the treatment of dislipidaemia, but they should not be used as first-line therapy. The CHMP has now confirmed those conclusions and recommended that fibrates not be used as first-line armamentarium, **except in patients with hypertriglyceridaemia, or who cannot take statins**. Regarding fenofibrate in particular, it should only be used in association with statins under special circumstances, namely whenever statins alone are not sufficient to adequately control lipid blood levels.

Finasteride
Risk of breast cancer in men?

In 2009, the European Pharmacovigilance Working Party (PhVWP) initiated an assessment on the risk of breast cancer in men taking finasteride. This assessment was prompted by cases of breast cancer reported during clinical trials and in the postmarketing period. Most cases were reported in relation to the 5 mg dose. However, there was a small number of cases associated with the 1 mg dose. Taking into account the available data, the PhVWP recommends that prescribers be aware of these new data and that **patients under treatment with finasteride** should be informed so that they immediately report any changes in their mammary glands, such as nodules, pain, gynecomastia, or mammary discharge.

Margarida Guimarães

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

Medicines Risk Management Dept. (Pharmacovigilance) at INFARMED I.P.
Ph.: 217 987 140 - Fax: 217 987 397
E-mail: farmacovigilancia@infarmed.pt

Northern Regional Pharmacovigilance Unit
Tel: 225 513 661 - Fax: 225 513 682
E-mail: ufn@med.up.pt

Centre Regional Pharmacovigilance Unit
Tel: 239 480 100 - Fax: 239 480 117
E-mail: ufc@aibili.pt

Lisbon and Tagus Valley Regional Pharmacovigilance Unit
Tel: 217 802 120 - Fax: 217 802 129
E-mail: uflvt@sapo.pt

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

Invirase® (saquinavir)
Lower dose in the first week

Invirase® (saquinavir) is an antiretroviral drug which is used in adults infected with HIV 1. It is given in combination with ritonavir and other antiretrovirals. It was approved in 1996 and is marketed in most EU countries, including Portugal. It is used by approximately one million patients each year.

In June 2010, the CHMP restricted the use of Invirase® in patients with risk factors for arrhythmia and/or conduction disorders, namely **long QT and PR intervals**. This measure followed on the results of a study conducted by the manufacturer. However, some doubts remained which have led the European Commission to require a global safety review.

The CHMP's conclusions confirm that the drug is effective and state that, although QT and PR interval prolongation has been seen in a clinical trial designed to evaluate these parameters, this safety signal has not been confirmed by the data obtained since saquinavir has been marketed. The risk of conduction disorders is proportional to the dose used, and is even greater in patients not previously exposed to this medicine. A **dose reduction during the first week of treatment** is therefore recommended in those patients who are being started on Invirase®.

INDEX CARD | **Director:** Júlio Carvalhal **Editor:** Rui Pombal **Assistant Editor:** Alexandra Pêgo **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

ADRs in Children
reported in Portugal in 2008

Introduction

Children are one of the subpopulations that are most vulnerable to the deleterious effects of medicines.

The physiology of children should not be construed as that of small-sized adults, and the toxicity profile of drugs in children is indeed different. There are significant differences in terms of pharmacokinetics, pharmacodynamics and frequency of occurrence of adverse effects when compared to adults. Other relevant factors include liver metabolism and kidney function immaturity, progressive development of organs, growth, sexual maturity, and diseases that are specific to children.

Adverse drug reactions (ADRs) are of great clinical importance and the literature points to an incidence of about 2 to 5 per cent of treated children. Furthermore, ADRs significantly add to healthcare costs. Nearly 5% of paediatric hospital admissions and 10% of paediatric inpatient conditions are related to problems associated with the use of medicines.

It has been extensively demonstrated that children are more sensitive to specific toxic effects of various drugs. Examples of such are the grey baby syndrome caused by liver immaturity affecting the metabolism of chloramphenicol, the association between aspirin and Reye's syndrome, liver toxicity associated with valproate, metabolic acidosis associated with propofol, and serious skin reactions associated with vigabatrin. Some ADRs present differently depending on the patient's age; metoclopramide, for instance, can cause dystonia in teenagers and parkinsonism in the elderly.

Pharmacovigilance mechanisms should be able to rise up to the specific challenges posed by paediatric safety data collection, including data on potential long-term effects.

Objectives and methods

This study aimed to characterise the profile of ADR reporting in children in Portugal. The spontaneous ADR reports received through the INFARMED National Pharmacovigilance System throughout 2008 were retrospectively analysed.

All spontaneous ADR reports occurring in Portugal and reported for the first time to INFARMED between 1 January and 31 December 2008 regarding children and adolescents younger than 18 years were included in the study. Spontaneous reporting in this country depends on the proactive action of three groups of health professionals – physicians, pharmacists and nurses. Spontaneous reports can also be sent in by Marketing Authorisation Holders (including cases published in the literature). Reports originating from clinical trials were excluded from the study.

For each ADR report (case), the following variables were studied: gender, age (as recorded in the database or calculated from the recorded date of birth), suspected medicine(s), ADR(s), outcome, and type of reporting professional.

The probability of the causal nexus between exposure to the suspected medicine and the ADR was not formally assessed.

The MedDRA (version 12.0) dictionary was used to code the ADRs according to SOCs (system organ classes). For each case, every reported ADR was analysed and coded by LLT (low level term - the most specific MedDRA level) in order to classify it under a primary SOC (less specific hierarchical level). More than one SOC was ascribed to those cases where the clinical manifestations fitted into multiple equally relevant SOCs.

The adapted ATC (Anatomical Therapeutic Chemical) Classification for active ingredients of suspected medicines was used.

Each spontaneous ADR report (i.e., each case) corresponds to a single child, but it may include one or more adverse reactions and/or one or more suspected medicines. Data from the cases reported in 2008 were updated whenever a follow-up report had been received until no later than the end of the first semester of 2009.

Results

The Portuguese National Pharmacovigilance System received **1654** reports of suspected ADRs in 2008. Of these, **136 (8.2%)** occurred in children aged 0 to 17 years.

Seriousness

Of all the cases in children, ninety-five (**70%**) were deemed **serious**. They included: hospital admission or prolongation of hospital stay (34.0%), temporary or definitive incapacity (3.2%), life threatened (11.6%), death (2.1%). In the remaining half of serious cases the reporting professional did not specify the criteria used.

Gender

53.8% (n=72) of the children were female, 46.2% (n=62) male. Sex was not recorded in two cases.

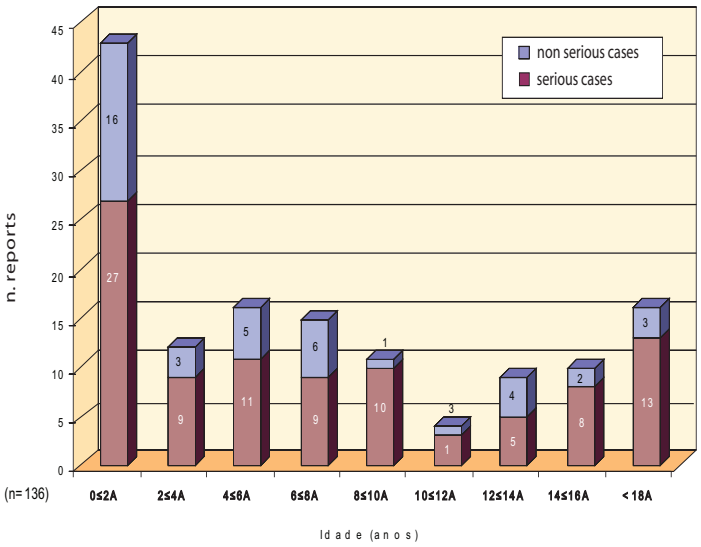

Chart 1. Spontaneous ADR reports in children (2008) – age group distribution.

Age

The greater number of reports corresponded to children in their **first year of life** - 22.1% (n=30), followed by children aged between 1 and 2 years – 9.6% (n=13) [Chart 1].

Of the total number of ADR cases, 52.2% (n=71) were in children younger than 6 years (pre-schoolers), 22.1% (n=30) in those aged between 6 and 11, and the remaining 25.7% (n=35) in adolescents (12 to 17 years of age).

In children younger than six, 66% of the cases were serious, as were 73% in children between 6 and 11 years, and 74% in adolescents (12-17 years).

SOC

213 primary SOCs were identified in the 136 cases of ADRs reported.

The commonest clinical manifestations were **cutaneous** (32.4%), **general disorders or conditions associated with the administration site** (16.4%), followed by gastrointestinal (12.2%), and immune system related (7%). Only 0.5% (1 case) was a suspicion of drug-related foetal malformation.

Within the subset of **serious** ADRs, **skin** disorders were also the most frequent ones (24.3%), followed by **gastrointestinal** manifestations (13.2%), and **immune** system disorders (9.9%).

ATC	total cases (n=145) [nº(%)]		serious cases (n=104) [nº(%)]	
J07 - Vaccines	49	(33,8%)	29	(27,9%)
J01 – Antibacterials for systemic use	23	(15,9%)	11	(10,6%)
N – Nervous system (excluding analgesics ATC N02)	17	(11,7%)	15	(14,4%)
N02;M01 – Analgesic and anti-inflammatory	15	(10,3%)	14	(13,5%)
L – Antineoplastics and immunomodulating agents	11	(7,6%)	11	(10,6%)
B – Blood and blood forming organs	7	(4,8%)	6	(5,8%)
R – Respiratory system	7	(4,8%)	6	(5,8%)
A – Alimentary tract and metabolism	6	(4,1%)	5	(4,8%)
G – Genitourinary system and sex hormones	2	(1,4%)	2	(1,9%)
S01 - Ophtalmologicals	2	(1,4%)	1	(1,0%)
C01 – Cardiac therapy	1	(0,7%)	1	(1,0%)
D - Dermatologicals	1	(0,7%)	1	(1,0%)
H02 – Corticosteroids for systemic use	1	(0,7%)	0	(0,0%)
J04 - Antimycobacterials	1	(0,7%)	1	(1,0%)
J06 – Immunosera and immunoglobulins	1	(0,7%)	0	(0,0%)
P02 - Anthelmints	1	(0,7%)	1	(1,0%)
Total suspected drugs	145	100%	104	100%

Table 1. Suspected medicines in ADR reports in children (2008).

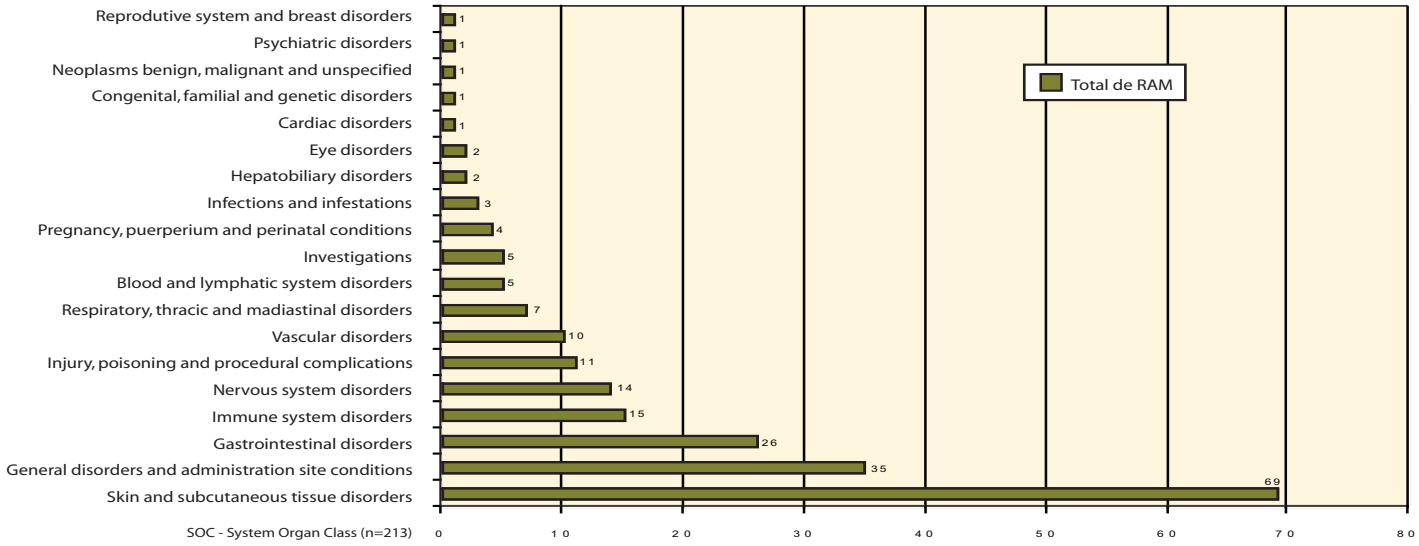

Chart 2. Spontaneous ADR reports in children (2008) – SOC distribution.

Suspected medicine

Several medicines were suspected in the ADRs reported in children. Table 1 highlights their groups according to the adapted ATC Classification. It should be noted that more than one suspected medicine may have been identified in some cases.

The suspected medicines most often reported for children were **vaccines** (33.8%), systemic **antibacterials** (15.9%), **central nervous system** drugs (analgesics excluded) (11.7%), and **analgesics and non-steroidal anti-inflammatory drugs** (10.3%).

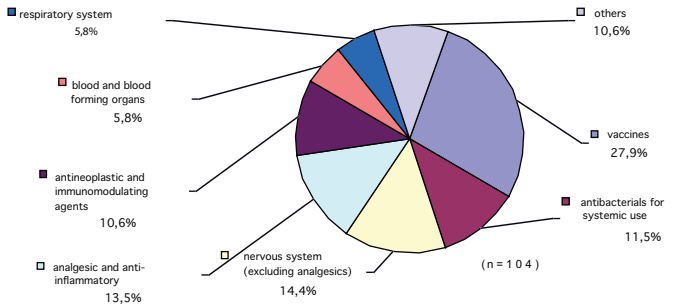

Chart 3. Groups of suspected medicines in serious cases of ADRs reported in children (2008).

In the **serious cases** [Chart 3], the most frequently reported medicines were again **vaccines** (27.9%), followed by medicines acting on the **central nervous system** (analgesics excluded) (14.4%) and **analgesics and non-steroidal anti-inflammatory drugs** (13.5%). Systemic antibacterials and antineoplastic and immunomodulator drugs came next (both 10.6%).

Type of reporting professional

Concerning the primary source of the reports, physicians were the health professionals who reported the most cases (50%), followed by nurses (32%) and pharmacists (5%).

Case evolution

Case evolution was determined as the updated reported clinical status at the time of study. In **72.1%** of children **cure** was reported, whereas 9.6% were recovering. In 1.5% cure with sequelae was recorded, and in 3.7% symptoms persisted without recovery.

Discussion

During the study period (2008), 136 spontaneous ADR reports in children younger than 18 years were received by the Portuguese National Pharmacovigilance System. They amounted to **8.2% of the total number of spontaneous ADR reports** (n=1654).

The comparability of the results obtained in this study is in general hindered by the scarcity of systematic data in paediatric populations worldwide, as well as by variability of methods used. Nevertheless, the Portuguese data seem to be in agreement with those from a study conducted in Spain [Morales-Olivas FJ et al], in which the proportion of cases in children (aged 0 to 14 years) was 9.8% of the annual general population total. The proportion inferred from the results of a Swedish study [Kimland E, et al] for cases in children (0 to 15 years) was higher (14.7%).

Children younger than one accounted for the greater percent of reports (22.1%), followed by toddlers aged between 1 and 2 (9.6%). This age group was also the one with most reported cases (52%) in a Danish study [Aagaard L et al]. In the USA, in a study on ADRs reported to the FDA in children younger than 2 years [Moore TJ et al], this age group corresponded to 1.1% of the total of ADRs in the general population.

In our study, the most common clinical manifestations were skin (32.4%), general or associated with the administration site (16.4%), followed by gastrointestinal (12.2%) and immune system related (7%). These rates are compatible with those from various other studies which show that the adverse effects most often reported are skin, gastrointestinal, central nervous system, psychiatric, general symptoms, and immune system.

Some of the most frequently reported drugs (antibacterials and vaccines, namely) are related to the treatment and prophylaxis of conditions that are common in these age groups – infectious and respiratory disorders. Analgesic/anti-inflammatory drugs (including for the symptomatic treatment of pyrexia) are also often used for infectious conditions.

Thus, vaccines (33.8%), systemic antibiotics (16.6%), central nervous system medicines (excluding analgesics) (11.7%), and analgesics and non-steroidal anti-inflammatory drugs (10.3%) were the groups most often described in ADRs in children. In the Swedish study, vaccines accounted for 63.8% of the reports, followed by antibacterials (10.1%) and drugs used for asthma (10.1%).

In Spain, antibiotics, drugs for respiratory system disorders and vaccines were the most reported suspected medicines. Antibiotics therefore, are consistently among the medicines most often implicated. In contrast, the relevant position described for medicines used in respiratory conditions is not mirrored by the Portuguese reporting profile.

It is essential that the detection and reporting of ADRs in paediatric populations be reinforced, especially in what concerns serious reactions, as well as those regarding novel medicinal products and recent paediatric indications.

An analysis of spontaneous ADR reports in children within a longer time frame will better define in the future the profile of spontaneous reports in Portugal.

References

- *Aagaard L et al. Adverse Drug Reactions in the Paediatric Population in Denmark. Drug Saf 2010; 33: 327-339*
- *Choonara I et al. Drug toxicity and surveillance in children. Br J Clin Pharmacol 1996; 42: 407–410.*
- *Clarkson A et al. Surveillance for fatal suspected adverse drug reactions in the UK. Arch Dis Child 2002; 87: 462–467.*
- *Impicciatore P et al. Incidence of adverse drug reactions in paediatric in/outpatients: a systematic review and metanalysis of prospective studies. Br J Clin Pharmacol 2001; 52: 77–83.*
- *Kimland E et al. Paediatric adverse drug reactions reported in Sweden from 1987 to 2001 Pharmacoepidemiol Drug Safe 2005; 14: 493–499.*
- *Moore TJ et al. Reported adverse drug events in infants and children under 2 years of age. Pediatrics 2002; 110: 1–5.*
- *Morales-Olivas FJ et al. Adverse drug reactions in children reported by means of the yellow card in Spain. J Clin Epidemiol 2000; 53: 1076–1080.*
- *Regulation EC No. 1901/2006 of the European Parliament and the Council of 12 December 2006 on Medicinal Products for Paediatric Use and Amending Regulation [online]. Available from URL http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2006:378:0001:0019:en:PDF [accessed 2010 Dec 14]*
- *Sammons HM et al. Clinical trials of medication in children, 1996-2002. Eur J Clin Pharmacol 2005; 61: 165-7.*

Tamoxifen
Variable clinical response

In 2009, the European Pharmacovigilance Working Party (PhVWP) conducted a review on the variability of clinical response to tamoxifen due to **genetic variants of CYP2D6**. This review preceded the publication of a series of studies which concluded that weak CYP2D6 metabolisers have lower plasma concentrations of endoxifen, one of the most important active metabolites of tamoxifen. The clinical data available suggest that tamoxifen's effectiveness in the treatment of breast cancer may be reduced in patients who are homozygotic for non-functional CYP2D6 alleles.

Given that tamoxifen is metabolised via CYP2D6, the concomitant use of **CYP2D6 inhibitors such as paroxetine, fluoxetine, quinidine, cinacalcet or bupropion**, should be avoided **if possible**, since according to some studies clinical response to tamoxifen may be impaired.

Margarida Guimarães

Somatropin 1
Increased mortality when used in doses higher than recommended?

The European Medicines Agency has started a safety review of all medicinal products containing somatropin 1 (recombinant growth hormone) after the French Agency had reported data from the Santé Adulte GH Enfant (SAGhE) epidemiological study suggesting there may be an increased risk of death in patients who have been taking somatropin since childhood (**for the treatment of growth hormone deficiency or low stature of unknown cause**), in comparison with the general population. The risk seems to be especially increased when **high doses** are used, namely above those recommended in the Summary of the Product's Characteristics. Based on this observational study only, it is not possible to ascribe the excess risk observed exclusively to somatropin. The results therefore, need to be confirmed and completed with **further studies**.

ADRs in the Literature...

Can ginseng protect against ototoxicity??

Cisplatin, an effective antineoplastic drug, can cause irreversible sensorineural hearing loss and serious tinnitus in humans. Cisplatin-induced ototoxicity is therefore a useful experimental model for ototoxicity. This study investigated the protective effects of Korean red ginseng extract on cisplatin-induced ototoxicity in auditory cells. Korean red ginseng extract seemed to play both an anti-apoptotic and anti-oxidative role on cisplatin-induced ototoxicity in the auditory cell line studied.

Im GJ, et al. Protective effect of Korean red ginseng extract on cisplatin ototoxicity in HEI-OC1 auditory cells. Phytother Res. 2010 Apr;24(4):614-21.

Interactions to keep in mind!

Anticoagulated Patients *

It is important to monitor the INR whenever a drug is started or discontinued in an anticoagulated patient.

A. INR monitoring makes risk relatively manageable:

Haemorrhage caused by increased antivitamin K effect (INR rise)

- amiodarone (dose-dependent and prolonged interaction: INR to be monitored over several months)
- antibiotics and azole antifungals
- antidepressants (amitriptyline, other imipramine drugs, serotonin reuptake inhibitors, and venlafaxin)
- antiepileptics such as valproic acid (see also below)
- cytotoxic antineoplastic agents (see also below)
- celecoxib (see also NSAIDs below)
- hypolipemic agents: fibrates, ezetimib
- sex hormones and anti-hormonal agents (e.g., tamoxifen, raloxifen, tibolone, flutamide, bicalutamide, danazole, testosterone)
- thyroid hormones
- alpha and beta interferons
- sugar-lowering sulphonamides
- Other: alopurinol, cisapride, colchicine, glucosamine, piracetam, orlistat, tramadol...
- Certain medicinal plants: garlic, cranberry, ginseng, Gingko biloba, Serenoa repens...

Decreased antivitamin K effect (INR drop)

- antineoplastic agents such as azathioprine and cyclophosphamide (see also above)
- cholestyramine
- enzyme inducers:
  antiepileptics such as carbamazepine and phenytoin
  antibiotics such as rifampin
  modafinil etc.
- sucralfate

Decreased or increased antivitamin K effect (INR drop or rise)

- alcohol
- anti-HIV agents
- corticoids
- oestroprogestative agents

B. Haemorrhagic episodes not predictable through INR monitoring:

- Acetylsalicylic acid *(antiplatelet effect)*
- NSAIDs *(antiplatelet effect)* (see also celecoxib above)
- Penicillin in high doses *(prolonged bleeding time, antiplatelet effect)*
- Certain ionic radiological contrast agents.

...

** Based on: la revue Prescrire*

BOLETIM ONLINE ADDRESS WITH ALL ISSUES SINCE 1998 :
www.infarmed.pt/portal/page/portal/INFARMED/ENGLISH
Click on Publications, then Boletim de Farmacovigilância year of issue.