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WHO Collaborating Centre for International Drug Monitoring

SIGNAL

Analyses of Adverse Reaction Reports in the WHO Database · June 2004

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- Lopinavir/ritonavir - Convulsions, convulsions aggravated, convulsions grand mal
- Tooth discolouration and herbal drugs
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the UPPSALA MONITORING CENTRE

All correspondence regarding signals presented in this document should go through *the* Uppsala Monitoring Centre

SIGNAL

Potentially interesting pharmacovigilance signals selected by the UMC Review Panel

The WHO has defined a signal as:
"Reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously" An additional note says: "Usually more than one report is required to generate a signal, depending on the seriousness of the event and the quality of the information".

A signal is therefore a hypothesis together with data and arguments. A signal is not only uncertain but also preliminary in nature: the situation may change substantially over time one way or another. A signal may also be more documentation which further qualifies a simple association of a drug product with an ADR, for examples, information on the range of severity of reaction, its outcome; postulating a mechanism; indicating an "at risk" group; a dose range which might be more suspect; or suggesting a pharmaceutical group effect or indeed a lack of such an effect by a particular drug.

SIGNAL is edited and produced by the Uppsala Monitoring Centre (UMC) and presents information derived from the WHO database. This database contains summaries of case reports of suspected adverse drug reactions, submitted by National Pharmacovigilance Centres (NCs) in about half the countries of the world. More information regarding these data, their limitations and proper use, is provided in the Caveat on the last page of this document.

The UMC Review Panel consists of international, experienced scientists, usually affiliated to a governmental or academic institution or a pharmaceutical company, invited by the UMC. They assess - under the responsibility of the UMC - the database for the occurrence of signals of possible importance for public health, drug regulation and science.

The topics discussed in SIGNAL are thus varying levels of suspicions derived from examination of the data in the UMC database. As emphasised above, SIGNAL contains different hypotheses, primarily intended to inform national regulatory authorities, which may in turn consider the needs for possible further action (for instance further evaluation of source data, or a study for the testing of a hypothesis). The distribution of SIGNAL by the UMC is currently restricted to NCs, regulatory authority staff and their advisers, participating in the WHO Collaborating Programme for International Drug Monitoring and to international pharmaceutical companies which can be identified as uniquely responsible for the drug concerned. The UMC takes no responsibility for contacting all market authorisation holders.

National authorities and NCs are responsible for deciding on further action including communicating the information in SIGNAL to relevant health professionals, and to the responsible market authorisation holders, within their jurisdictions.

In order to further a healthy debate, we encourage all recipients of SIGNAL to comment briefly (about 700 words) on individual topics. The comments will be published in the next available edition.

Edwards I.R, Biriell C. Harmonisation in pharmacovigilance.
Drug Safety 1994;10:93-102.

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Source information

IMS LIFECYCLE April 2004 has been used as a source of information regarding the licensor/patent holders, to which certain signals have been submitted for comments.

Responses from industry
Responses from industry are unedited. The calculations, analysis and conclusions are theirs, and should be given serious but critical consideration in the same way as any scientific document. The WHO, and UMC, is not responsible for their findings, but may occasionally comment on them.

Levofloxacin – Deafness, hearing decreased

Levofloxacin is the levorotatory (S) enantiomer of racemic ofloxacin, a fluoroquinolone antibiotic compound. It has broad-spectrum activity against many Gram positive and negative bacteria, and finds clinical use in a range of common infections of the urinary tract, skin, and respiratory tract (upper and lower). It is also a second-line agent in tuberculosis. The IC values for levofloxacin increased to 0.92 (IC-2sd 0.35) for 'Deafness', and 2.06 (IC-2sd 1.40) for 'Hearing decreased' during 2003-4.

Literature

Levofloxacin, like most of the fluoroquinolones, has been documented as a cause of a spectrum of central nervous system disorders such as headache, tremor and dizziness, but of greater significance is the propensity to induce encephalopathy, increased intracranial pressure and convulsions. However, it was not possible to identify many published reports associating levofloxacin (or other fluoroquinolones) with ototoxicity, as manifested by deafness or tinnitus, except for the Health Canada publication of four serious case reports of deafness or decreased hearing suspected to be associated with ciprofloxacin (not found in Vigibase).[1] They involved men aged 35, 47, 65 and 67 years old. Three were receiving 1000 mg/d orally and one was receiving 800 mg intravenously. In all cases, the reactions began within 1 week after initiation of therapy. Three patients recovered, and the fourth experienced partial permanent deafness. Another publication reports the decreased hearing of a patient receiving ofloxacin.[2] On the other hand there are other articles finding no association with ototoxicity for ofloxacin.[3]

The UK SPC states 'visual and auditory disturbances' under Neurological effects.[4] The PDR lists earache and tinnitus as adverse events.[5]

Case reports

The 43 reports on these two critical terms originate from eight countries: USA (25 +1 suspected duplication), Germany (8), Finland (3), Canada (2), Sweden (1), Belgium (1), United Kingdom (1) and South Africa (1). A slight majority of the patients were female (25), whilst two reports stated no gender. The age varied from 16-90, with a great predominance in the age group of 50-80. Four patients recovered, six recovered with sequelae, four patients had not recovered by the time of reporting. One patient died and the reactions may have been contributory. Dechallenge was performed in eight cases, and the result was negative in five patients and positive in three patients. Two of the cases were causality assessed as probable and five were considered possible.

Time to onset, where stated, was reported to be between 3-7 days for the majority of the patients, but there were single cases of 1, 2, 9 and 10 days, and even one case of 4 months.

Indications for levofloxacin treatment, when stated, included cystitis (2), pneumonia (2), 'viral infection in conditions classified elsewhere, unspecified' (1), 'other prophylactic chemotherapy' (1), nephrolithiasis (1), 'diarrhoea, not otherwise specified' (1), 'sinusitis, acute not otherwise specified' (1) and 'ear infection, not otherwise specified' (1). On two

other reports no indication was given, but the concomitant drugs were decongestant or benzyl penicillin, possibly implicating a sinusitis and or ear infection.

Most cases implicate levofloxacin as the only suspected drug, either oral or intravenous or both (n=37), but four cases had co-suspected drugs reported: phenylephrine hydrochloride (HCl)/guaifenesin/phenylpropanolamine HCl, gentamicin and two other fluoroquinolones (ofloxacin and ciprofloxacin). Except for the co-suspected aminoglycoside gentamicin, the reports do not appear to be confounded by the presence of concomitant (known) ototoxic drugs.

Discussion

This lack of published data increases the significance of the current series of 42 cases of levofloxacin for intensive review. Please note that a number of these cases may be confounded by the fact the deafness or hearing loss may be associated with the condition for which the drug is being given, namely acute otitis media or acute sinusitis (which can lead to blockage of the Eustachian tubes and diminished hearing).

The precise degree of confounding cannot be ascertained as in many instances, the reason for using the levofloxacin is not stated in the case report. Furthermore, a number of the patients are elderly (> 65 years old; n=18) and some may be experiencing some degree of presbyacusis; an aggravation of pre-existing hearing loss may nevertheless be a factor in some patients, and cannot simply be dismissed.

In conjunction to the clinical review of the cases for levofloxacin it became apparent that there are a number of reported cases on terms within the System Organ Class Hearing and vestibular disorders, for other fluoroquinolones, as can be seen in table 1.

Table 1. ‘Hearing and vestibular disorder’ terms reported for fluoroquinolones.

Adverse Drug Reaction	Al	Ci	En	Fl	Ga	Gr	Le	Lo	Mo	No	Of	Pe	Ru	Sp	Te	Tr
DEAFNESS	1	71	1		1	2	25	4	6	15	46	1	1	1	3	9
DEAFNESS NERVE		1							3	1	1					
EAR ACHE		13		1	2		2	5			9				1	4
EAR DISORDER NOS		20	1		1		3		4		8				2	2
HEARING DECREASED	1	41	1		2	1	19		12	3	17	2				10
HYPERACUSIS							2				6					
OTOTOXICITY		2					2		1							
TINNITUS	1	102	3	2	7		15	8	21	21	61	3	1	1	5	15
VESTIBULAR DISORDER		11			2		1	1		2	11				1	1

Al = alatrofloxacin, Ci = ciprofloxacin, En = enoxacin, Fl = fleroxacin, Ga = gatifloxacin, Gr = grepafloxacin, Le = levofloxacin, Lo = lomefloxacin, Mo = moxifloxacin, No = norfloxacin, Of = ofloxacin, Pe = pefloxacin, Ru = rufloxacin, Sp = sparfloxacin, Te = temafloxacin, Tr = trovafloxacin

Conclusion

Despite the possibility of an alternative explanation in some of the cases, the association of levofloxacin and deafness appears to be an early signal and warrants some ongoing monitoring.

Signal from the Centre.

References

1. Ciprofloxacin: suspected association with deafness and reduced hearing. Canadian Adverse Reaction Newsletter, Volume 14, Issue 1, January 2004.
2. Visus- und Hörverlust als Komplikation der Therapie mit Ofloxacin. Brensing KA, Rüddel H, Schmieder RE, Schulte W Med Welt 1989;40:748-51.
3. A Benefit-Risk Assessment of Ofloxacin Otic Solution in Ear Infection. Wai TKH, Tong MCF Drug Safety 2003:26(6):405-420.
4. http://www.medicines.org.uk/searchresult.aspx?search=levoflox
5. PDR on-line (2004.06.22)

Lamotrigine and alopecia

Lamotrigine, a phenyltriazine compound, is an antiepileptic used as monotherapy or as an adjunct to treatment with other antiepileptics.

Skin rash and serious skin reactions including Steven Johnson syndrome and toxic epidermal necrolysis (TEN) are known adverse drug reactions (ADRs) for lamotrigine. The main risk for these ADRs appears to be with concomitant use with valproate (includes valproic acid and divalproex sodium) and when exceeding the dosage recommendations. In addition, the risk appears to be greater in children[1].

Alopecia or related terms were not listed in Martindale[1], the Summary of Product Characteristics (SPC) for the UK and Sweden, or the Drugdex[2] in May 2004. In the Physician's Desk Reference (PDR)[3], alopecia was stated to infrequently have been reported as an adverse event in clinical trials. The publication 'Reactions Weekly' has not included any narrative with the combination and a search in PubMed revealed only one case of scarring alopecia as a complication to toxic epidermal necrolysis that had been caused by lamotrigine[4]. This review was undertaken since the question, if lamotrigine could give rise to alopecia, was raised by the Swedish National Centre.

The WHO data base contained 98 reports in May 2004 with the combination lamotrigine and alopecia (IC value 1.43, IC-2std 1.14 = fourth quarter of 2003) and nine reports with hypotrichosis (IC -1.18, IC-2std -2.09). No noticeable duplicates were found among the reports. The combination, lamotrigine and alopecia are primarily summarised below and a short summary was made for the nine reports with hypotrichosis.

Reports of alopecia for lamotrigine have continuously been entered into the WHO data base since 1994 with between 8 and 14 reports per year.

Number of reports by country

The reports originated from the United Kingdom (40), Australia (10), Denmark (10), United States (10), Germany (8), South Africa (4), Sweden (4), Switzerland (3), Canada (2), Netherlands (2), Austria (1), Belgium (1), Ireland (1), Norway (1), and Spain (1).

Age and gender

Seventy-eight patients were female, 15 were male, and five reports lacked information about gender. Among the reports that included age (85 reports), the average age was 32 years with a range between 5 and 81 years old. Ten of the cases were below 12 years old, 11 were between 12 and 17 years old, 36 were between 18 and 39, and 28 were between 40 and 81 years old.

Suspected drugs

A total of 87 reports included lamotrigine assessed to be the single suspect drug by the reporter. Eleven reports were assessed to be co-suspected with valproic acid (5), carbamazepine (2), diazepam (1), reboxetine (1), levetiracetam (1), amisulpride (1), and vigabatrin (1, co-suspected with valproic acid). In Martindale[1], hair loss is labelled for valproic acid and carbamazepine, and alopecia for vigabatrin.

Signal from the Centre.

Co-reported drugs

Lamotrigine was reported as the only drug for 35 reports, and 63 reports included co-reported concomitant or suspect drugs. Forty-three reports included concomitant or co-suspected drugs that are labelled causing alopecia. For 23 reports, valproic acid was reported as concomitant (18) or as suspect drug (5), and carbamazepine was included for 12 reports either as concomitant (10) or as suspect drug (2).

Co-reported events

For 68 patients alopecia was reported as the single event. The co-reported events for the other 30 patients were most commonly central and peripheral system disorders and psychiatric disorders. Serious co-reported events were Steven Johnson syndrome, encephalopathy, hepatic failure, and hepatitis. There was one South African patient with acquired hypothyroidism who received levothyroxine where the National Centres' causality assessment between lamotrigine and alopecia was unlikely. Three other patients also received levothyroxine which indicate that the patients suffered from thyroid disorders. Another patient received iron supplements which could be an indication of iron deficiency or nutritional deficiency which might have resulted in alopecia.

The National Centres' causality assessments

For the reports where the National Centres had assessed causality, 33 reports were possible (21) or probable (12) and three reports were assessed as unlikely.

Doses of lamotrigine

The initial adult dose for use as monotherapy is 25 mg once daily, thereafter a continuous increase of dose is made until the usual maintenance doses of 100 to 200 mg daily is reached[1]. Some of the patients have required up to 500 mg daily. The dose-regimen of lamotrigine for use as an adjunct to therapy with enzyme-inducing antiepileptics (but not with valproate) is different starting with a higher dose and having a higher maintenance dose (200-400 mg/day). Of the reports with information about doses of lamotrigine (73 reports), there were 25 reports with a dose above 200 mg per day of which nine reports included a dose above 400 mg per day.

Reports with dechallenge, rechallenge and outcome information

Information about dechallenge was unknown for 73 reports, dose was not changed for 16, and drug was withdrawn with the reaction abating for nine reports. One of the 98 patients was reported to have a positive rechallenge. The female patient was from Switzerland. No information about age, treatment dose or dates. Outcome information was not available for 38 reports, five patients recovered with sequelae, 13 patients recovered, and 42 patients were recorded not to have recovered at the time of report.

A subset of cases

The following table presents the 20 cases where the onset of alopecia was after drug start (or the same day) and where lamotrigine was the only reported drug. Information about rechallenge was either unknown or not done for these 20 cases. The majority of these cases had alopecia onset after more than 3 months of lamotrigine use, six patients were below 20 years old, and eight patients had a daily dose above 200 mg.

Signal from the Centre.

Table 1. Reports with lamotrigine reported as the only drug and with onset of alopecia after drug start (or the same day)

Country & Report id	Age/ Sex	Lamotrigine administration data (dose in mg)	ADR onset/ Outcome	Preferred Term	Dechallenge & Causality
BEL 8130188	50/F	1995-20010126 (200)	20010126/ Recovered	Alopecia, Amnesia	Positive dechallenge, Possible
DEN 1724870	29/F	19950714 - (300)	199601/ Not recovered	Alopecia	DNC, Probable
DEN 1627975	23/F	19941020 - (600)	199507/ Recovered with sequelae	Alopecia	DNC, Probable
DEN 1763540	17/F	19960612 - ()	199609/ Recovered with sequelae	Alopecia	DNC, Probable
DEU 8234638	45/F	200109 - ()	200203/ Not recovered	Alopecia	Unknown, Not (yet) assessed
DEU 1374946	43/F	19920220-19940701 (500)	19931201/ Recovered	Alopecia	Positive dechallenge, Possible
DEU 1371999	30/F	199310- (800)	199310/ Not recovered	Alopecia	DNC, Possible
ZAF 2439213	27/F	19990401- (200)	19990601/ Not recovered	Alopecia	DNC, Possible
ZAF 2439214	22/M	199811- (200)	19990701/ Unknown	Alopecia	DNC, Possible
SWE 2768219	47/F	20010123-20010518 (100)	200105/ Recovered	Alopecia	Positive dechallenge, Possible
SWE 1842110	13/F	1995-1999 (600)	1996/ Recovered	Alopecia, Hepatic enzymes increased, Sweating increased, Weight increased	Positive dechallenge, Not assessable
SWE 8096769	12/F	200001- (350)	2002/ Not recovered	Alopecia	Unknown, Possible
GBR 2769850	7/F	20010504- (50)	20010510/ Not recovered	Alopecia, Urinary incontinence	Unknown, -
GBR 1855158	44/M	19960708- (200)	19970118/ Not recovered	Alopecia	Unknown, -
GBR 2435870	38/F	19970821- (275)	19991215/ Not recovered	Alopecia	Unknown, -
GBR 2050113	30/M	19960914- (100)	19980612/ Unknown	Alopecia	Unknown, -
GBR 2435862	18/F	19980901- (350)	19991215/ Unknown	Alopecia	Unknown, -
GBR 2287176	15/F	19990715- (150)	19990901/ Not recovered	Alopecia	Unknown, -
USA 2892879	45/F	19980101- ()	19980101/ -	Alopecia, Anxiety, Visual field defect	Unknown, -
USA 8250351	34/F	20020518-20020928 ()	20020901/ -	Alopecia	Not stated, -

DNC = Dose not changed

Signal from the Centre.

Reports with hypotrichosis

In addition to the 98 reports with alopecia, there were 9 reports with hypotrichosis, all from the USA. For all but one patient, lamotrigine was reported as the single-suspect drug. Primidone and valproic acid were reported as co-suspected drugs for one patient.

Ages were between 29 and 69 years but for five patients age was lacking. There were five female, two male and two reports that lacked information about gender.

Conclusion

In the majority of cases, the reporter had assessed lamotrigine to be the single suspect drug. However, many reports included co-reported drugs that might cause alopecia. Only a few reports of serious events in addition to alopecia were reported and several cases with alopecia were assessed, by the national centres, to be possibly or probably related to lamotrigine.

Lamotrigine is already known to cause serious skin reactions. This signal indicates that alopecia could be another, although less serious, skin problem for lamotrigine.

References

1. Sweetman S (Ed), Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic version,
Thomson MICROMEDEX, Greenwood Village, Colorado, (Edition expires [6/2004]).
2. Lamotrigine. In: Klasco RK (Ed): DRUGDEX® System. Thomson MICROMEDEX, Greenwood Village, Colorado (Edition expires [6/2004]).
3. Lamictal Chewable Dispersible Tablets (Lamotrigine), Manufacturer. Physicians' Desk Reference (electronic version), Thomson MICROMEDEX, Greenwood Village, Colorado (Edition expires [6/2004]).
4. Sullivan JR, Watson A. Lamotrigine-induced toxic epidermal necrolysis treated with intravenous cyclosporine: a discussion of pathogenesis and immunosuppressive management. Australas J Dermatol. 1996 Nov; 37(4):208-12.

Lopinavir/ritonavir – Convulsions, convulsions aggravated, convulsions grand mal

Kaletra® is a combination of two protease inhibitors, lopinavir and ritonavir. Ritonavir is present only in low dosage, not for its antiviral effects but for its potent ability to interfere with the cytochrome P-450 metabolism (especially 3A4) of lopinavir thereby greatly increasing the blood levels and bioavailability of the latter. The IC value for the combination of lopinavir/ritonavir and the critical term 'Convulsions aggravated' was, during the fourth quarter of 2003, 1.76 (IC-2sd 0.46) and that led us to perform a clinical review of the case reports.

Literature

Convulsions have been documented with ritonavir, but to date, no similar published findings have been identified for lopinavir. This could be due to the fact that lopinavir has not been marketed for as long as ritonavir, or because it is genuinely less epileptogenic.

The PDR lists convulsions under the adverse events section, but the European SPC does not mention anything in the section for 'Undesirable effects'. They have however stated that patients should be monitored for ADRs related to propylene glycol toxicity, e.g. seizures, under the 'Special warnings…' section.

Case reports

The reports originated from the United States (9), Canada (1) and the United Kingdom (1). All, but one, of the patients were male and the age ranged between 32 and 45, except two patients, that were 80 years of age. Time to onset varied from nine days, up to one or more months and even one case of over one year.

Discussion

The current series of 11 cases is not very detailed, and is somewhat confounded by the presence of other drugs used in HIV infection, including lamivudine, saquinavir, stavudine, emtricitabine and others. None of these drugs has been documented as having major epileptogenic potential. One patient was also receiving an unknown dosage of penicillin, which has been associated with convulsions. HIV patients can also have different underlying diseases that may affect the neurology of the patient.

Taken together as a group, these 11 cases are nevertheless suggestive of an early signal that the combination of lopinavir and ritonavir, even though in a low concentration, may do more than just boost the bioavailability of lopinavir: the combination may increase the neurotoxicity or proconvulsive effects of either or both drugs, to a degree not seen in the pre-approval clinical studies.

In addition when looking at all the drugs within the Anatomical Therapeutic Chemical classification group of J05AE 'Protease inhibitors', there are some more reports on aggravated convulsions and grand mal (see table 1).

Signal from the Centre.

Table 1. Reports on different protease inhibitors and convulsion terms.

Adverse Drug Reaction	Number of reports
Amprenavir	
CONVULSIONS	7
CONVULSIONS GRAND MAL	2
Atazanavir	
CONVULSIONS	1
Indinavir	
CONVULSIONS	28
CONVULSIONS AGGRAVATED	1
CONVULSIONS GRAND MAL	3
Nelfinavir	
CONVULSIONS	11
CONVULSIONS AGGRAVATED	1
CONVULSIONS GRAND MAL	2
Ritonavir	
CONVULSIONS	32
CONVULSIONS AGGRAVATED	1
CONVULSIONS GRAND MAL	9
CONVULSIONS LOCAL	1
Ritonavir/Lopinavir	
CONVULSIONS	6
CONVULSIONS AGGRAVATED	4
CONVULSIONS GRAND MAL	2
Saquinavir	
CONVULSIONS	19
CONVULSIONS AGGRAVATED	2
CONVULSIONS GRAND MAL	8
CONVULSIONS LOCAL	1

Conclusion

The association of protease inhibitors and aggravation of convulsions appears to be an early signal and is worth watching for a time to see if more cases emerge to strengthen this suspicion.

Tooth discolouration and herbal drugs

Hydrastis Canadensis[1-3]

In 2000 a mother observed a yellowish discolouration of the teeth of her almost four-year-old daughter after the oral administration of Gingivitol N (hydrastis canadensis, Hennig Arzneimittel, Germany). Dose and duration were not specified, but according to the reporting paediatrician the relationship was 'probable'. The company had not previously received similar reports, but a second case of tooth discolouration in association with Gingivitol N was reported in 2003. The latter report came from a pharmacist and, apart from the addition "perhaps caused by the alkaloid berberin", it unfortunately does not contain any further information.

Hydrastis Canadensis is a native plant of Canada and the Western part of the USA. The vernacular common name "Golden Seal" refers to its bright yellow root-stock. It contains isoquinoline alkaloids, mainly hydrastine, berberine, and canadine (= catrahydroberbe), and with lesser amounts of related alkaloids. Products from hydrastis Canadensis are thought to have stimulating properties, improve the appetite and aid digestion, have anti-bacterial and anti-protozoan properties, and to be helpful in dyspepsia, gastric catarrh, gastric ulceration and vomiting of pregnancy. Its roots should not be harvested before 4 years. Berberine is also present in other plants, including Berberis vulgaris (barberry) and the Chinese herb Huanglian, and is thought to have cardiovascular effects. Hydrastis has since long been used as a yellow hair colouring agent. In Gingivitol it is used for healthy gums, as a 'dental plaque inhibitor'.

Cynara Scolimus[4-5]

This case report concerned a 55-year-old woman who noticed a dark discolouration of her teeth whilst using Hepar SL Forte capsules for self-medication. She could not remove the discolouration with a tooth brush, but it disappeared after she stopped taking the drug. Cynara scolimus (artichoke) contains a large variety of chemicals and is said to have a stimulatory action on bile secretion and use for dyspeptic complaints. Cynara scolimus is popular for its pleasant bitter taste which is attributed mostly to a phytochemical called cynarin found in the green parts of the plant. Cynarin, a caffeoylquinic acid, is considered one of artichoke's main biologically active chemicals. In the UMC database there is one case report of tooth discolouration and cynara scolimus (Hepar SL Forte, Sertürner Arzneimittel, Germany). Cynara scolimus containing products occasionally elicit contact dermatitis or other allergic reactions. The occurrence of tooth discolouration is not established.

Senna Alexandrina[6]

There are two case reports of young girls (3 and 6 years old) with tooth discolouration attributed to the use of senna alexandrina fruit (Senokot Westminster Laboratories); one from Australia and one from the USA. Although liquid paraffin was taken by one, there were no other drugs, known to cause tooth discolouration.

Alexandrian senna consists of the dried leaflets of Cassia acutifolia, a small shrub indigenous to the middle and upper Nile territories. The constituents of senna leaves are not yet well known. Anthraglucosennin is the name given to a mixture of substances

obtained by exhausting senna with weak ammonia, precipitating with hydrochloric acid, drying the precipitate, exhausting with alcohol, and evaporating to dryness. It contains senna-emodin, C15H7O2(OH)3, which appears to be identical with aloe-emodin. There some suggestions that it may contain a colouring ingredient. The leaves of the senna plant are pale greyish-green in colour. The urine may be given a yellow colour by senna, which changes to red on the addition of an alkali.

Conclusion

These five case reports raise the suspicion that the use of some herbal drugs might affect the colour of the teeth. Such products may contain dyes that could precipitate in the dental plaque or attach to the dental surface. More information regarding the possible dental effects of herbal drugs is needed.

References

1. http://www.botanical.com/botanical/mgmh/g/golsea27.html
2. http://www.dominionherbal.com/herbs_month/Goldenseal.htm
3. Lau CW, Yao XQ, Chen ZY, Ko WH, Huang Y. Cardiovascular actions of berberine. Cardiovasc Drug Rev. 2001 Fall;19(3):234-44.
4. http://www.rain-tree.com/artichoke.htm
5. http://www.innvista.com/health/foods/vegetables/artichok.htm
6. http://www.ibiblio.org/herbmed/eclectic/bpc1911/cassia.html

Signal from Dr Myles Stephens, United Kingdom.

Sirolimus and pulmonary haemorrhage

Introduction

Sirolimus is an immunosuppressive agent. Sirolimus is a macrocyclic lactone produced by Streptomyces hygroscopicus and is indicated for the prophylaxis of organ rejection in patients receiving renal transplants. It is recommended that sirolimus be used initially in a regimen with cyclosporine and corticosteroids. Sirolimus inhibits T lymphocyte activation and proliferation that occurs in response to antigenic and cytokine (Interleukin [IL]-2, IL-4, and IL-15) stimulation by a mechanism that is distinct from that of other immunosuppressants. There are 34 reports stored in the WHO-UMC database of haemorrhage involving the respiratory system: epistaxis, pulmonary haemorrhage, and haemoptysis. (May 2004). The IC values for the different combinations with sirolimus can be seen in table 1.

Table 1. IC-values for combinations with sirolimus during the 4th quarter of 2003.

ADR	IC	IC-2sd	Total number of combinations
Epistaxis	1,29	0,48	12
Haemoptysis	2,64	1,86	13
Pulmonary haemorrhage	3,08	2,28	12
Respiratory tract haemorrhage	0,92	-1,14	1

Literature

Two relevant abstracts have been published:

- Sirolimus-associated diffuse alveolar haemorrhage. Vlahakis et al. Mayo Clinic Proceedings. 79(4):541-5, 2004 Apr. Abstract: Sirolimus is an immunosuppressive medication used in transplant recipients. To our knowledge, we describe the third reported case of alveolar haemorrhage in association with sirolimus. Fever, dyspnoea, haemoptysis, and lung infiltrates resolved rapidly with cessation of sirolimus therapy both initially and after reinstitution of the drug. Unlike previous reports, our patient had no evidence of lymphocytic alveolitis but rather marked macrophage haemosiderosis, suggesting that sirolimus pulmonary toxicity may manifest through 2 separate mechanisms. Our case highlights an uncommon but potentially lethal manifestation of sirolimus pulmonary toxicity.
- Sirolimus-associated pulmonary toxicity. Pham et al. Transplantation. 2004 Apr 28;77(8):1215-1220. BACKGROUND: Pulmonary toxicity has recently been recognized as a potentially serious complication associated with sirolimus therapy. We further detail this condition on the basis of our own cases and those reported in the literature. METHODS: We report three cases of suspected sirolimus-induced pulmonary toxicity that occurred in three renal transplant recipients and searched PubMed for all previously reported cases. RESULTS: Including our current cases, 43 patients with sirolimus-induced pulmonary toxicity have now been reported. Clinical data were incomplete in 28 cases. Analysis of available data for 15 patients revealed that the most commonly presenting symptoms were dyspnoea on exertion and dry cough followed by fatigue and fever. Chest radiographs and high-resolution computed tomography scans commonly revealed bilateral patchy or diffuse alveolo-interstitial infiltrates.

> Bronchoalveolar fluid analysis and lung biopsy in selected case reports revealed several distinct histologic features, including lymphocytic alveolitis, lymphocytic interstitial pneumonitis, bronchoalveolar obliterans organizing pneumonia, focal fibrosis, pulmonary alveolar haemorrhage, or a combination thereof. The diagnosis of sirolimus-associated pulmonary toxicity was made after an exhaustive work-up to exclude infectious causes and other pulmonary disease. Sirolimus discontinuation or dose reduction resulted in clinical and radiologic improvement in all 15 patients within 3 weeks. CONCLUSION: The temporal relationship between sirolimus exposure and onset of pulmonary symptoms in the absence of infectious causes and other alternative pulmonary disease and the associated clinical and radiologic improvement after its cessation suggests a causal relationship. Because the use of sirolimus in organ transplantation has become more widespread, clinicians must remain vigilant to its potential pulmonary complication.

The PDR acknowledges that sirolimus can cause thrombocytopenia. Under 'adverse *events* were reported with >/=3% and <20% incidence in patients' are: Haemic and Lymphatic systems: ecchymosis, leucocytosis, lymphadenopathy, polycythemia, thrombotic thrombocytopenic purpura (hemolytic-uremic syndrome); Cardiovascular: haemorrhage. Respiratory: epistaxis.

The European SPC lists epistaxis as a common adverse reaction, but also mentions cases of interstitial lung disease for sirolimus.

Medline Plus warns that some side effects can be serious: 'The following symptoms are uncommon, but if you experience any of them or those listed in the IMPORTANT WARNING section, call your doctor immediately: pale skin, unusual bleeding or bruising, cough, shortness of breath'.

Case reports

There are 34 cases, one of which is probably a duplicate. The 33 cases can be divided into those with epistaxis and those with pulmonary haemorrhage/ haemoptysis/ respiratory tract haemorrhage. Sirolimus was the single suspect drug in 29 reports and five other drugs were co-suspected. The case report data is summarized in tables 2, 3 and 4.

Table 2. Countries of origin.

Country of origin	Number of reports
United States	27 (+ one possible duplication)
Spain	3
Germany	1
Belgium	1
Australia	1

Table 3. Gender of the patients.

Gender	Number of reports
Male	23
Female	9
Unknown	1

Signal from Dr Myles Stephens, United Kingdom.

Table 4. Age range of the patients.

Age range	Number of reports
< 10	1
11-20	2
21-30	3
31-40	4
41-50	7
51-60	12
61-70	0
= 71	2
Unknown	2

There are nine cases of epistaxis of which five cases were associated with thrombocytopenia. Four cases are rated as possible. Eleven cases of haemoptysis, 11 cases of pulmonary haemorrhage and one case or respiratory tract haemorrhage were reported. Two cases had both haemoptysis and pulmonary haemorrhage. These 23 cases (if caused by sirolimus) may represent either the Pham or Vlahakis mechanisms. Of these 23 cases there are nine cases of pulmonary haemorrhage, and one case of both pulmonary haemorrhage and epistaxis, which I think should be rated as possible (table 5). Only one of these refers specifically to the presence of thrombocytopenia.

Table 5. Case reports of pulmonary haemorrhage rated 'Possible'.

NC	Age Sex	ADR	Co-suspected (S) or concomitant (C)	Time to onset	NC info on sirolimus	Conclusion
USA	52 F	pulmonary haemorrhage	gemfibrozil, insulin, **omeprazole**, prednisolone	15 weeks	Positive dechallenge	The fact that the reporter said that the prime suspect was sirolimus suggests that omeprazole may have been a long-term therapy.
USA	60 M	cardiac arrest, respiratory tract haemorrhage, death	-	45 days	-	The sequence of events is not known but the haemorrhage is likely to have preceded the cardiac arrest and therefore sirolimus is a possible cause
USA	47 F	haemoptysis, pulmonary haemorrhage, dyspnoea, respiratory failure	amlodipine, metoclopramide, sulfamethoxazole /**trimethoprim**, **tacrolimus**	4 months	Positive dechallenge	There are three candidates: sirolimus, tacrolimus and trimethoprim. The mechanism could be similar to that in the Pham or Vlahakis papers.
USA	36 M	mitral valve incompetence, pneumonia, haemoptysis, dyspnoea, embolism pulmonary, lung infiltration	-	3 months	-	The pneumonia, haemoptysis, dyspnoea, lung infiltration would fit the condition described by Pham, but? unrelated to the mitral valve incompetence or pulmonary embolism. If we knew the sequence of events diagnosis would be easier.

Signal from Dr Myles Stephens, United Kingdom.

BEL	57 M	pneumonitis, haemoptysis	**S: tacrolimus**, amiodarone HCl C: simvastatin, sodium bicarb, calcium carb, nystatin, methyl-prednisolone, sulfamethoxazole/ **trimethoprim**, **omeprazole**	7 weeks	Indication: Kidney transplant. Not recovered	Negative dechallenge to amiodarone, and the fact that all other drugs were continued, is against a drug cause, but it could represent a similar ADR as in the Pham or the Vlahakis papers, which was unrecognised.
AUS	51 F	pulmonary haemorrhage pulmonary infiltration, anaemia, fever	C: **tacrolimus**, prednisolone, **acetylsalicylic acid,** atenolol	15 months	Not recovered	This would fit with a pulmonary vasculitis, but is similar to the Pham or Vlahakis cases
DEU CT	42 M	haemoptysis, pneumocystis carinii infection	bisoprolol, prednisone, alfacalcidol, amlodipine	25 days	Indication: disorder immune mechanism, Recovered	Pneumocystis carinii occurs in the immuno-suppressed patients and although bleeding is not mentioned in the textbook as a symptom it must be a possible cause. The recovery must have been due to treatment that is not mentioned.
SPA	-	vomiting, abdominal pain, haemoptysis, renal function abnormal	-	-	Indication: Kidney transplant	The haemoptysis seems unconnected with the other events; Sirolimus was unlikely to have been prescribed alone. In view of the lack of information the causality must remain possible
USA	46 M	chest x-ray abnormal, dyspnoea, coughing, pulmonary infiltration, haemoptysis, fever, diarrhoea	Insulin, nystatin, prednisone, hydromorphone, **pentamidine,** metoprolol **gangciclovir,** rosiglitazone.	-	-	But for the diarrhoea all these events fit with Pham/Vlahakis picture.
USA	58 M	wound dehiscence, tachycardia, thrombocytopenia, sepsis, anaemia (rbc?), pulmonary haemorrhage, bacterial infection (pseudomonas), pneumothorax, pleural effusion, coma, bacterial resistance, ischaemic necrosis, multiple organ failure, healing impaired, immune system disorder, hypoxia, hypotension, malaise, epistaxis, alkalosis, atrial fibrillation	C: Prednisone, Sulfamethoxazole /**Trimethoprim, Amiodarone**, Lansoprazole, **Tacrolimus**	-	-	The pulmonary haemorrhage + epistaxis + thrombocytopenia suggests the latter as the cause. There are three alternative drug candidates.

Drugs causing thrombocytopenia are in **bold**
Drugs which interact with Sirolimus giving increased drug levels are <u>underlined</u>
NC = National Centre
CT = Clinical trial

Signal from Dr Myles Stephens, United Kingdom.

Mechanisms

The Vlahakis paper suggests as a mechanism: macrophage haemosiderosis. Whilst the Pham paper includes lymphocytic alveolitis, lymphocytic interstitial pneumonitis, bronchoalveolar obliterans organizing pneumonia, focal fibrosis, pulmonary alveolar haemorrhage. The background of thrombocytopenia in the epistaxis cases suggests a third mechanism.

The lack of detail prevents us making a distinction between a Pham syndrome and a Vlahakis syndrome.

Conclusion

It is probable that thrombocytopenia sometimes causes epistaxis. Pulmonary haemorrhage can probably be caused by another mechanism confirming the Pham and Vlahakis papers. Whether or not thrombocytopenia interacts with Pham/Vlahakis mechanisms is not clear, but it could theoretically occur.

Signal from Dr Ruth Savage, New Zealand.

Can infliximab aggravate a silent breast cancer?

Infliximab is a monoclonal antibody that is directed against tumour necrosis factor alpha (TNF-alpha). It is used in the treatment of such disorders as Crohn's disease and rheumatoid arthritis where the disease is severe and unresponsive to other disease-modifying agents. *The* UMC database holds 32 reports of malignant breast neoplasm occurring in female patients taking infliximab. The IC is 3.14 (IC-2sd 2.63) for the fourth quarter of 2004. The IC has been stable at approximately this level for the last four quarters analysed (2003-3: IC 2.82, IC-2sd 2.21; 2003-2: IC 3.03, IC-2sd 2.42; 2003-1: IC 2.78, IC-2sd 2.07).

Analysis of the reports reveals that two are duplicates, thus 30 cases have been reported. Of these 24 were from the USA, three from Canada, two from Spain and one from Sweden. There were 20 reports of malignant breast neoplasm and 10 of aggravated malignant breast neoplasm. Because the reports were of a malignancy there was no useful outcome or dechallenge data in these reports. The age range of the women was 38 to 79 years. Two were aged less than 50 years, thirteen were 50 to 64 years old and eleven were aged over 64 years. Age was not stated for four women. The indication for use was only stated for 4 patients. Three woman aged 38, 53 and 54 years were treated for Crohn's disease and a 49 year old woman for psoriasis.

The length of time from the start of infliximab treatment to diagnosis was given for 13 patients. For a cluster of 7 patients duration ranged from 3 to 6 months. For the other six the duration to onset was 54 days, 10, 11, 14.5, 20 and 24 months. Those with aggravated breast cancer did not show a consistently shorter duration to onset compared with those with a new diagnosis. There were very variable periods between time of the last exposure and diagnosis and some women were continuing to use infliximab.

Other medicines were listed for 22 patients although few dates were given. Six women were taking hormone replacement therapy (HRT), five of these were taking medroxyprogesterone with conjugated oestrogens and one was taking oestradiol. It is well recognised that HRT increases the risk of breast cancer. Nineteen women were taking other immunomodulators as well as infliximab. Sixteen were taking methotrexate, three were taking azathioprine, two hydroxychloroquine, three leflunomide and one ciclosporin. Three women, two with aggravated breast cancer, were taking two or more immunomodulators. Of the three women taking leflunomide one had septicaemia. One woman with aggravated breast cancer was reported to have died due to lung metastases. As well as infliximab she was taking leflunomide and hormone replacement therapy.

In the database there are reports of a number of different malignancies in association with infliximab use, in particular lymphomas, colorectal cancer, breast cancer and skin cancers. Malignancies with infliximab have been previously discussed in a SIGNAL issue (1). There is published evidence for an increased risk of lymphoma in patients with rheumatoid arthritis and for lymphoma and colorectal cancer in Crohn's disease. One of the risk factors in these patients is prolonged use of immunosuppressants. However there is no evidence for an increased risk of breast cancer with these disorders (2).

Signal from Dr Ruth Savage, New Zealand.

It is notable that one third of the reports were of aggravated breast cancer. Given the short duration of infliximab use prior to diagnosis of breast cancer in most of the patients it is likely that if there is a relationship between infliximab use and breast cancer it is an aggravating rather than an inducing effect.

In deciding whether there is a signal that infliximab may aggravate breast cancer the following evidence needs to be considered. Both lymphoma and solid tumours occurred in patients in clinical trials of infliximab. The incidence of solid tumours including breast cancers was estimated to be commensurate with the expected incidence for the populations studied (2, 3). Animal studies have not provided good evidence that blocking TNF-alpha is likely to lead to carcinogenesis (2). Furthermore infliximab is not a general suppressant of immune function and does not suppress lymphotoxin-alpha (TNF-beta) that lyses tumour cells (2). However, in a recent study from the Mayo clinic of 500 patients with Crohn's disease treated with infliximab, nine patients developed malignancies (4). Three of these, a pulmonary adenocarcinoma, a metastatic lung cancer and a lymphoma were considered possibly related to infliximab because of the temporal relationship between its administration and the development of first symptoms.

Within *the* UMC database the infliximab/breast cancer combination shows a statistically significant degree of disproportionality. However, clinical significance is difficult to assess as the natural history of cancer means that there is no good dechallenge and rechallenge data in the case reports.

Of interest therefore is a comparison between infliximab and leflunomide. The latter inhibits pyrimidine synthesis, has immunomodulating and antiproliferative properties and, like infliximab, is indicated for severe rheumatoid arthritis. In *the* UMC database there are 5390 reactions reported for infliximab and 3119 for leflunomide. These medicines both first occurred in the database in 1999 and it is therefore of interest to compare their adverse reaction profiles. There are no reports of breast cancer with leflunomide as the suspect medicine. This lends support to there being a signal for infliximab that should be further examined. However in two infliximab reports leflunomide was listed as a concomitant medicine and there is no clear reason why it should not also have been suspect. Thus there may be awareness amongst prescribers that there may be a link between infliximab and carcinogenesis thus promoting reporting of breast cancer with infliximab but not leflunomide.

The signal is weak because of the short duration of exposure, because of the use of hormone replacement therapy and other immune modulators by many of the women and the difficulty of getting useful case report data in disorders such as cancer. However the epidemiological evidence that there is no increase in risk of breast cancer with infliximab is currently derived from the possibly inconsistent method of comparing incidence in clinical trials with that in relevant healthy populations. This signal indicates a need for more formal studies.

Signal from Dr Ruth Savage, New Zealand.

References

1. WHO Signal, March 2002, pp14-15.
2. Cohen RB, Dittrich KA. Anti-TNF therapy and malignancy – a critical review. Can J Gastroenterol 2001;15(6): 376-384.
3. Remicade for intravenous injection. Centocor Inc 2003. Physicians' Desk Reference entry.
4. Colombel J-F, Loftus EV, Tremaine WJ. The safety profile of infliximab in patients with Crohn's disease: the Mayo Clinic experience in 500 patients. Gastroenterology 2004;126:19-31.

Editorial comment:
Since this assessment was made one more case has been reported to Vigibase. The patient was a female from United Kingdom with a malignant neoplasm in the breast after infliximab treatment.

Signal from Dr David Clark, New Zealand.

Bosentan and cardiac arrest

Bosentan is an antagonist of the powerful vasoconstrictor released from the vascular endothelium: endothelin-1. It is presently indicated for the management of pulmonary hypertension.

Eighteen case reports are reviewed of bosentan associated with cardiac arrest (12 female and 6 male) that are listed on the total WHO-UMC database. In five of these cases the outcome was death: in two cases it was noted that the 'reaction might have been contributory. Fifteen of the reports were from the USA with one from Canada and two from Germany. The most recent IC value (2003, fourth quarter) is 1.76 (IC-2sd 1.07) with the previous IC being 1.65 (IC-2sd -0.68).

Cardiac arrest is not listed in drug information sources examined (Martindale, PDR, DrugDex on-line in June 2004). A Medline literature search did not reveal any associations of bosentan associated with cardiac arrest as an adverse reaction.

Other suspected drugs and concomitant therapy

In all except 3 of the cases bosentan was the single suspected drug. In the 3 cases where a second suspect drug was listed, in one the other suspected drug was celecoxib, in another cyclophosphamide and in the other, a 16 year female, promethazine was also suspected.

Although in only one case was an indication provided ('primary pulmonary hypertension'), it is likely that in most the indication was the indicated (WHO) use of grade III-IV pulmonary hypertension. Patients prescribed bosentan are thus likely to be seriously ill with other concomitant illness, including cardiac failure, and may be prone to cardiac arrest associated with the indication. Thus in many cases, several concomitant medications were listed with many of these also likely to have been prescribed to help control the pulmonary hypertension (calcium channel blockers, prostaglandin analogues, sildenafil, diurectics), other disease associated with pulmonary hypertension or to reduce the risk of the development of such disease. Such drugs included warfarin, aspirin and other drugs affecting platelet function, beta-blockers, digoxin, various bronchodilators and oral and inhaled glucocorticoids. Surprisingly, in none of the 18 cases were any drugs listed as interacting.

Causality assessment

In two of the 18 cases both onset of treatment and onset of reaction were given and in these cases the onset of reaction was 11 and 48 days respectively, after commencing treatment.

Effects of drug dechallenge were not recorded and outcome information was provided for only five of the cases. Four of the fatal cases noted 'Died - reaction may be contributory' and an additional case had sudden death as an ADR term. The final case with outcome information stated 'recovered with sequelae'. Overall the data is insufficient to enable causality assessment.

Signal from Dr David Clark, New Zealand.

Comment

This association has a positive IC value which has increased from that from the previous quarter. All but three of the 18 case reports were from the USA and unfortunately the quality of the information provided is low, with most reports not providing necessary information for causality assessment.

Although causality can not be established, in view of the severity of this possible reaction and the increasing IC, monitoring of bosentan should be continued, hopefully with more complete data supplied from some National Centres, to help establish the strength of this life-threatening association.

Signal from Dr David Clark, New Zealand.

Iomeprol and cardiac arrest

Iomeprol is an iodinated non-ionic contrast medium that is used for radiographic procedures and has been on the market since 1994.

Ten case reports listed on the total WHO-UMC database are reviewed where iomeprol was associated with cardiac arrest (4 male and 6 female). In two of these cases (one male and one female), the outcome was 'died - reaction might have been contributory'. Three reported 'recovered' and one 'recovered with sequelae'. Of the remaining reports, outcome was noted as 'unknown' in three reports and in the other it was not stated.

Six of the reports were from Germany, two from France and one each from Italy, and Japan. The IC value during the fourth quarter of 2003 was 1.37 (IC-2sd 0.49) with the previous IC being 1.40 (IC-2sd 0.52).

Although cardiac arrest is not specifically listed as an adverse reaction associated with iomeprol in drug information sources examined (Martindale, DrugDex on-line), DrugDex noted that 'adverse effects involving the cardiovascular system' occurred with contrast agents. Cardiac arrest is recognised as a rare adverse effect associated with the older ionic contrast media (e.g. amidotrizoic acid: Martindale on line). A retrospective analysis of over 10,000 patients in a catheterization laboratory (Holm et al., 2001) indicated that adverse reactions to contrast media were recorded in a total of 107 (1.1%) patients and that both ionic and non-ionic (including iomeprol) contrast media participated equally in the reactions with no difference observed in the type of reaction. The reactions included ventricular fibrillation in 76 (0.75%) and cardiac arrest in 12 (0.12%).

Other reactions in addition to cardiac arrest

In eight cases other reactions were noted in addition to cardiac arrest and some of these were suggestive of a severe hypersensitivity reaction. They included respiratory arrest/insufficiency/depression (6 cases); circulatory failure; bradycardia; flushing; laryngeal oedema; anaphylactic shock; coma; nausea and erythema.

Other suspected drugs, concomitant therapy

Iomeprol was the single suspected drug in nine cases: in the other dobutamine was administered; presumably to help manage the cardiac arrest. In the only case where other concomitant drugs were listed these were: oestradiol, progesterone and lacidapine.

Causality assessment

This association has a positive IC value which has remained constant over the previous two quarters. Dechallenge occurred in three cases, two from Germany and one from Italy. In the two cases from Germany the 'reaction abated' following dechallenge and the patients 'recovered'. In the third case, from Italy, the reaction abated and the patient 'recovered with sequelae'.

Signal from Dr David Clark, New Zealand.

National centres assessed causality as 'possible' in three cases, including the two above cases from Germany with dechallenge information, and a third also from Germany where the outcome was recorded as 'died – reaction may be contributory'. In the above case from Italy, the National Centre causality assessment was 'probable'. National Centre causality assessments were not available for the remaining cases. Not surprisingly, drug rechallenge information was not available.

The dates of administration and onset of reaction were provided in 4 cases and in three of these cases the onset was on the same day as administration. In two of these cases (the above case from Italy and one from France) the outcome was 'died - reaction may be contributory' and in the other the patient 'recovered with sequelae'. In the other case, from Japan, the time to onset was 12 days following administration and the outcome was recorded as 'recovered'. Thus, in the few cases where they could be determined, onset times were consistent with causality. It is plausible that the reaction could result from chemical action on tissues or that it could be a rare manifestation of a hypersensitivity reaction.

Table 1. A summary of case reports of cardiac arrest after iomeprol treatment.

Country Year	Age Sex	Admin. data	Co-suspected (S) or concomitant (C) drugs	ADRs	Outcome; NC comments
JPN 1996	61 M	100 ml i.v.	-	Cardiac arrest, respiratory arrest	Recovered; Treatment continued, dose not changed
DEU 1996	64 M	241 ml i.v. one time	-	Cardiac arrest	Died – reaction may be contributory; Causality: Possible
DEU 1997	53 F	i.v.	-	Cardiac arrest, bradycardia, flushing, respiratory insufficiency	Unknown; Causality: Not (yet) assessed
FRA 1998	63 F	i.v. for one day	C: estradiol, progesterone, lacidipine	Cardiac arrest, respiratory arrest	Died – reaction may be contributory
DEU 1998	60 F	i.v.	-	Cardiac arrest, respiratory depression, larynx oedema	Unknown; Not (yet) assessed
DEU 1999	63 M	i.v.	-	Cardiac arrest, respiratory depression, circulatory failure, nausea	Unknown; Not (yet) assessed
FRA 2000	35 M	120 ml i.v. in total	S: dobutamine i.v.	Cardiac arrest	-
DEU 2003	- F	80 ml i.v. one time	-	Cardiac arrest, coma	Recovered; Causality: Possible; Positive dechallenge
DEU 2003	26 F	i.v.	-	Cardiac arrest, respiratory depression, anaphylactic shock	Recovered; Causality: Possible; Positive dechallenge
ITA 2003	72 F	120 ml i.v. one time	-	Cardiac arrest, erythema	Recovered with sequelae; Causality: Probable; Positive dechallenge

Signal from Dr David Clark, New Zealand.

Comment

The above information, together with the positive IC values and evidence from the literature that cardiac arrest is associated with non-ionic (including iomeprol) as well as ionic contrast media (Holm et al., 2001), provide a strong signal that iomeprol is associated with cardiac arrest. Although this reaction is likely to be rare, it is important that radiologists be aware that serious reactions, including cardiac arrest, are possible.

Reference

Holm F, Aschermann M, Hornig A, Simek S, Linhart A, Humhal J. Komplikace podani kontrastnich latek v katetrizacni laboratori: petileta retrospektivni studie. [Complications in administration of contrast media in the catheterization laboratory: a 5-year retrospective study]. Vnitr Lek 2001 Jul;47(7):444-449.

Signal from Dr Ed Napke, Canada.

Sirolimus/Tacrolimus - Abortion

We have three reports of abortion occurring during the concomitant use of sirolimus and tacrolimus, all from the USA. In two cases the women had previous normal pregnancies, resulting in normal children: now the women aborted and had a miscarriage. One case, there was an abortion eight months after cessation of taking the immune suppressing drug. This is a signal to alert practitioners to the possibility of the linkage and request them to report past and current experiences. The IC value for sirolimus and abortion was, during the fourth quarter of 2003, 0.50 and the IC-2sd -0.79.

Case 1

This was a spontaneous report from a nurse. A female aborted her pregnancy while on sirolimus. Concomitant drug was tacrolimus. No dates or doses given.

Case 2

This patient was a 36 years old female, who had a renal transplant approximately June 2001, with a past history of two full term deliveries and no premature deliveries. Therapy of sirolimus started June 2001. Dose not specified. Concomitant drug was tacrolimus. The patient become pregnant June 25/2001. An ultrasound August 21/2001 revealed a missed abortion-gestation 7 weeks. Foetal pathology was unremarkable.

Case 3

A 27 year old female was on sirolimus. The drug was given orally, 2 mg once per day, for liver transplantation. She has a 5 year old child. Concomitant therapy was tacrolimus. The patient was reported pregnant February 2001. Sirolimus was stopped. In March 2001 she experienced a miscarriage. 8 months after stopping sirolimus she was 2.5 months pregnant and experienced another miscarriage in January 2002. The past history includes encephalopathy and autoimmune hepatitis.

Sirolimus

The PDR states that sirolimus is embryo-/fetotoxic in rats and in combination with cyclosporine, rats had increased embryo-/fetal mortality compared with sirolimus alone.[1] The text also states that sirolimus should be used during pregnancy only if the potential benefit outweighs the potential risk to the embryo/fetus. The UK SPC states that effective contraception must be used during sirolimus therapy and for 12 weeks after sirolimus has been stopped.[2]

Tacrolimus

Both PDR and DrugDex state that tacrolimus is transferred across the placenta and have been associated with neonatal hyperkalaemia and renal dysfunction.[1, 3] In a retrospective case analysis of 100 pregnancies in 84 women receiving tacrolimus prior to and during gestation, where 12% were spontaneously aborted.[4] Vigibase does not contain further reports regarding tacrolimus and the specific term abortion. It does include two reports with death foetal.

Signal from Dr Ed Napke, Canada.

More information regarding the use in humans of sirolimus and tacrolimus during pregnancy is needed.

References

1. PDR on-line
2. Http://emc.medicines.org.uk
3. DrugDex on-line
4. Kainz A, Harabacz I, Cowlrick IS, Gadgil S, Hagiwara D. Analysis of 100 pregnancy outcomes in women treated systemically with tacrolimus. Transpl Int. 2000;13 Suppl 1:S299-300.

Ectopic pregnancy and etonogestrel implants
Response from Organon

Implanon (Org 32222) is a subdermal progestogen-only contraceptive implant containing the synthetic progestogen etonogestrel (ENG, 3-ketodesogestrel). After subdermal insertion of Implanon in the upper-arm a continuous, slowly decreasing release of ENG occurs, providing contraceptive protection for three years. The contraceptive efficacy of Implanon is superior to that of combined oral contraceptives due to the combination of a very high degree of ovulation inhibition and independence of compliance.

Recently, the Uppsala Monitoring Centre (UMC) of the WHO has prepared a SIGNAL on the risk of ectopic pregnancy during use of etonogestrel implants[1]. The view of the Marketing Authorization Holder (MAH, NV Organon) on this SIGNAL is summarized below.

In our opinion, the current Implanon labelling adequately reflects the post marketing surveillance data reported for Implanon.

Controlled clinical trials with Implanon

Traditional progestogen-only pills (POPs) allow ovulation in 15-85% of cases and rely for contraceptive efficacy mainly on progestagenic effects on the cervical mucus and the endometrium. Unintended pregnancies among POP users are more likely to be ectopic, possibly due to reduced activity of the fallopian tube.

The absolute rate of ectopic pregnancies is of course markedly decreased in women using POPs compared to the absolute rate in fertile women not using contraception. However, in the small fraction who become pregnant while using the progestin-only pills, the proportion of which is ectopic is possibly increased.

In the Clinical Development Program with Implanon, no in-treatment pregnancies were observed, and therefore the relative risk of ectopic pregnancy was not calculable.

UMC database 'SIGNAL'

The UMC database has, by using the BCPNN (Bayesian Confidence Propagation Neural Network) methodology and after stratification for age and gender, found a statistically significant increased reporting rate of ectopic pregnancies with the use of etonogestrel implants in women 17-69 years of age (Information Component (IC) =2.89; IC 2sd=1.96). The raw estimate for the IC is 3.56 (IC-2sd=2.78).

Although we highly appreciate the efforts of the WHO/UMC to signal possible relationships between adverse events and medicinal products, interpretation should be made with care. Apart from general considerations (see WHO backgrounders), for Implanon several more specific reservations can be made.

Firstly, the UMC database contains spontaneously reported suspected adverse reactions (ADRs) to pharmaceutical products. Reporting rates are dependent on several factors

(e.g. uncertainty that the ADR is definitely caused by the drug, the length of time a drug has been marketed, severity of the disease, recent media attention, etc). It seems not unlogical that a prescriber may be more likely to report an ectopic pregnancy as an ADR when his/her patient is using a contraceptive method than when she is using another (non-hormonal) drug e.g. an antibiotic or NSAID. Consequently, reporting rates of ectopic pregnancies to contraceptive methods, including progestogen-only contraceptives, may be disproportionally higher than reporting rates of ectopic pregnancies to other drugs.

Secondly, the description of the methods highly suggests that in the analysis no restrictions have been made for the reference group with regard to the class of exposed drugs. It may be obvious that the reference group includes ADR-drug combinations with non-hormonal drugs to which ectopic pregnancies are less likely to be reported. Consequently, using all drugs as reference, a signal of ectopic pregnancies with contraceptive methods will be overestimated.

Thirdly, ectopic pregnancies will obviously not be reported in males or in women who are not of fertile age. Comparing reporting rates of ectopic pregnancies in contraceptive users with a reference group that includes these males and women will clearly overestimate the IC. Consequently, the raw IC is higher that the IC stratified for age and gender. Further, the stratum of interest (17-69 years) still includes women who are not of childbearing age.

Post marketing surveillance data reported to Organon

Until March 1, 2004, Organon received 711 medically confirmed cases of unintended pregnancies associated with Implanon, of which 28 ectopic pregnancies (including at least 12 of the 13 UMC reports that resulted in generation of the 'Signal'). This total number of pregnancy cases corresponds to a very low overall pregnancy rate of less than 0.05 per 100 implants sold. In 398 of these cases the implant may have been present during conception, including 24 ectopic pregnancies (6%). In 79 of the 398 cases it is clear from the available data that the woman conceived while Implanon was in situ, including 12 ectopic pregnancies (15%).

The rate of ectopic pregnancies calculated for Implanon during post-marketing surveillance (6-15% of all unintended pregnancies) is lower than the rate reported for IUDs (25-50%)[2] and in agreement with the rates reported in clinical studies with either Norplant (Norplant: 10%, Norplant II: 14%)[2] or POPs (7%)[3]. However, in these clinical studies the exclusion of women with risk factors for ectopic pregnancy may have produced a bias toward underestimation of the proportion of ectopic pregnancies[2].

Implanon product labelling

Ectopic pregnancy is a serious and often life-threatening condition. As with other progestagen-only contraceptives, the relative risk of ectopic pregnancies as a percentage of the total number of pregnancies is higher among Implanon-users as compared to the general population, but the absolute risk with Implanon is lower as Implanon is highly effective in the prevention of pregnancy. This is reflected in the current Implanon labelling implemented world-wide:

"The protection with traditional progestagen-only contraceptives against ectopic pregnancies is not as good as with combined OCs, which has been associated with the

frequent occurrence of ovulations during the use of these methods. Despite the fact that Implanon® consistently inhibits ovulation, ectopic pregnancy should be taken into account in the differential diagnosis if the woman gets amenorrhea or abdominal pain.[i]"

In our opinion, the current Implanon labelling adequately reflects the post marketing surveillance data reported for Implanon.

References

1. The Uppsala monitoring Centre. Ectopic pregnancy and use of etonogestrel implants. WHO SIGNAL April 2004:5-6.
2. Furlong I-A. Ectopic pregnancy risk when contraception fails: A review. J Reprod Med Obstet Gynecol 2002;47:881-5.
3. MacCann MF, Potter LS. Progestin-only 'oral' contraception: a comprehensive review. Contraception 1994;50:S9-S195.

[i] Source: Implanon Company Core data Sheet RA 0450 CCDS 5 (5.0)

Editorial comment:
The IC calculation using a background consisting of reports on contraceptives only, also would have lead to highlighting this combination for clinical review (IC 1.46, IC-2sd 0.74).
We have also, unusually, made a minor editorial addition to the Organon statement, by putting quotation marks around the core data sheet information, for clarity, because it is split on two pages.

Infliximab and intestinal obstruction
Response from Johnson & Johnson

The WHO signalling group has observed a potential signal for intestinal obstruction for infliximab (Remicade®). Twenty-one reports of intestinal obstruction, which were revealed in a search of the WHO database from 2000 to 2003, were commented on in WHO Signal, April 2004. Additionally, through 2004, potentially there are 51 reports (including possible duplicates) of intestinal obstruction associated with infliximab use in the WHO database.

Intestinal obstruction is listed in the Company Core Data Sheet as an adverse event in the Summary of ADRs in Clinical Trials based on the ACCENT II (Fistulizing Crohn's disease) Integrated Summary of Safety. Additionally, the J&J Worldwide Safety Database was reviewed for such event. Based on the postmarketing data, a clear association of the event to infliximab therapy could not be known with certainty as a large majority (approximately 80% when indication was known) of the cases involved Crohn's disease. Intestinal obstruction is a frequent complication of Crohn's disease without infliximab treatment, thus, confounding interpretation of the postmarketing data. Other confounding factors (e.g., long-term use of corticosteroids or concomitant medications associated with obstruction or effects on peristalsis) were also identified.

To conclude, intestinal obstruction is a listed event in the Company Core Data Sheet. In country labels for Remicade, such as the USPI under Summary of ADRs in Clinical Trials, intestinal obstruction is labelled. The SPC lists intestinal stenosis under Summary of ADRs in Clinical Trials.

Lansoprazole and severe cutaneous reactions
Response from Takeda

Severe cutaneous reactions, "Stevens-Johnson syndrome (SJS)" and "Toxic epidermal necrolysis (TEN)", have already been listed in the lansoprazole core safety information based on postmarketing experience and are included in the official labelling in the EU, USA and Japan. Since the International Birthdate (December 1990), lansoprazole has been marketed for more than 10 years in a total of 98 countries. As of the end of 2002, cumulative patient exposure is estimated to be approximately 200 million patients, representing 23 million patient-years. This vast amount of exposure gives the incidence as 0.8/million patient-years for TEN/SJS associated with lansoprazole, which is comparable to the reported incidence of TEN/SJS, 0.93-6.1/million patient-years, in the general population. [1-3]

Takeda will continue to monitor this suspected adverse drug reaction as part of safety surveillance henceforth.

References

1. Strom BL et al., A population-based study of Stevens-Johnson syndrome. Incidence and antecedent drug exposures. Arch Dermatol. 1991 Jun; 127(6): 831-8.
2. Schopf E et al., Toxic epidermal necrolysis and Stevens-Johnson syndrome. An epidemiologic study from West Germany. Arch Dermatol. 1991 Jun; 127(6):839-42.
3. Roujeau JC et al., Toxic epidermal necrolysis (Lyell syndrome). Incidence and drug etiology in France, 1981-1985. Arch Dermatol. 1990 Jan; 126(1):37-42.

The BCPNN

What it is, what it does and how to interpret the numbers it generates

The BCPNN methodology

The BCPNN (Bayesian Confidence Propagation Neural Network) methodology uses a neural network architecture to measure dependencies between drugs and adverse reactions within the WHO database. The BCPNN can be used to detect unexpected patterns in the data and to examine how such patterns vary over time. The BCPNN is using a measure of disproportionality called the Information Component (IC).

The Information Component (IC)

The Information Component (IC), as used here, is a measure of the strength of the quantitative dependency between a drug and an ADR. A positive IC value indicates that a particular drug-adr combination is reported to the database more often than expected from the rest of the reports in the database. An IC value of zero means that there is no quantitative dependency while a negative IC value indicates that the combination is occurring less frequently than statistcally expected in the database. The higher value of the IC, the more the combination stands out from the background.

The IC value is based on:

- the total number of case reports with drug X (Cx); and
- the total number of case reports with adverse reaction term Y (Cy); and
- the number of reports with the specific drug-ADR combination (Cxy); and
- the total number of reports in the database (C).

New data may cause the IC to either increase or decrease. When the IC is calculated from large numbers, a new report is less likely to cause a fluctuation in the IC value. The standard deviation for each IC provides a measure of the robustness of the value. The larger the Cx, Cy and Cxy values are, the narrower the confidence interval. The IC-2std (IC minus two standard deviations) is the value of the lower 95% confidence limit for the IC.

Interpretation of the IC

The IC does not give any information about the qualitative causality of a drug-adr combination. The IC shows quantitative dependencies based on the reports in the WHO database.
If the IC value increases over time and the IC-2std value is positive, the likelihood of a positive quantitative association between the drug and the adverse reaction is high, although clinical assessment remains essential.

References:
Bate A, Lindquist M, Edwards IR, Olsson S, Orre S, Lansner A, De Freitas RM. A Bayesian neural network method for adverse drug reaction signal generation. European Journal of Clinical Pharmacology 1998;54:315-321.

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Caveat Document

Accompanying statement to data released from the WHO Collaborating Centre

The WHO Collaborating Centre for International Drug Monitoring, Uppsala, Sweden receives summary clinical reports about individual suspected adverse reactions to pharmaceutical products from National Centres in countries participating in a Collaborative Programme. Only limited details about each suspected adverse reaction are received at the Centre. It is important that the limitations and qualifications which apply to the information and its use are understood.

The term "pharmaceutical product" is used instead of "drug" to emphasize that products marketed under one generic or trade name may vary in their content of active or other ingredients, both in time or from place to place.

The reports submitted to the Collaborating Centre in many instances describe no more than suspicions which have arisen from observation of an unexpected or unwanted event. In most instances it cannot be proven that a pharmaceutical product or ingredient is the cause of an event.

The reports, which are submitted to National Centres, come from both regulatory and voluntary sources. Some National Centres accept reports only from medical practitioners; other National Centres accept reports from a wider spectrum of health professionals. Some National Centres include reports from pharmaceutical companies in the information submitted to the Collaborating Centre; other National Centres do not.

The volume of report for a particular pharmaceutial product may be influenced by the extent of use of the product, publicity, nature of reactions and other factors which vary over time, from product to product and country to country. Moreover, no information is provided on the number of patients exposed to the product.

Thus the sources of reports accepted by National Centres vary, as do the proportions.

A number of National Centres which contribute information to the Collaborating Centre make an assessment of the likelihood that a pharmaceutical product causes the suspected reaction. Other National Centres do not document such assessments on individual reports in the WHO Database.

Processing time varies from country to country. Reporting figures obtained from the Collaborating Centre may therefore differ from those obtained directly from National Centres.

For the above reasons interpretations of adverse reaction data, and particularly those based on comparisons between pharmaceutical products, may be misleading. The information tabulated in the accompanying printouts is not homogeneous with respect to the sources of the information or the likelihood that the pharmaceutical product caused the suspected adverse reaction. Some describe such information as "raw data". Any use of this information must take into account at least the above.

Some National Centres which have authorized release of their information strongly recommend that anyone who intends to use it should contact them for interpretation.

Any publication, in whole or in part, of the obtained informations must have published with it a statement:

(i) of the source of the information

(ii) that the information is not homogeneous at least with respect to origin or likelihood that the pharmaceutical product caused the adverse reaction,

(iii) that the information does not represent the opinion of the World Health Organisation.

Omission of these 3 statements may exclude the responsible person or organization from further information from the system.

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