

RESTRICTED



WHO Collaborating Centre for
International Drug Monitoring

SIGNAL

Analyses of Adverse Reaction Reports in the WHO Database • May 2005



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.

Abacavir- myocardial infarction

Abacavir is a nucleoside reverse transcriptase inhibitor structurally related to guanosine analogue carbovir with antiretroviral activity, used in the treatment of Acquired Immune Deficiency Syndrome (AIDS) caused by Human Immune deficiency Virus (HIV). The use of reverse transcriptase inhibitors in the treatment of AIDS is normally associated with other antiviral treatments, specially the protease inhibitors. For these later one, the cardiovascular risk has been already identified, mainly related to the occurrence of myocardial infarction and the increase in atherosclerotic plaques.¹ However, there is no published evidence of myocardial infarction and ischemia in connection with reverse transcriptase inhibitors treatments.²

At the time of the assessment (2004:2) there are 34 cases of Myocardial infarction reported to the database (Table 1) (seven possible duplicate reports), with an IC value of 1.81 (IC025 = 1.33). In three cases death was related to the ADR. The cases show no particular age trends, and were sent by six different National Centres. It is important to remark that in 20 cases abacavir was associated with protease inhibitors that could play a substantial role in the occurrence of the ADR. Nevertheless, there are nine cases of myocardial infarction where abacavir is not co-reported with protease inhibitors. Even though it can not be ruled out that these patients have not been on protease inhibitors prior to the treatment of abacavir, this was not reported. In four of the cases where abacavir was reported without protease inhibitors, one positive dechallenge was reported. One case even presents a positive rechallenge (despite the paucity of data recorded).

There is not a particular trend of other associated ADR in these cases and only three patients were reported having chest pain as co-morbidity: myocardial ischaemia (1), chest pain (4), angina pectoris (1), pain in limb (2), ST elevated (1), increased myoglobin (1), coronary artery disorder (3), increased cardiac enzymes (1), cardiac arrest (3), ventricular fibrillation (1), hypokinesia (1), dyspnoea (3), pulmonary oedema (1), Adult Respiratory Stress Syndrome (1), pulmonary haemorrhage (1), laryngeal oedema (1), headache (1), nausea (1), hypokalemia (1), arthralgia (1), hypersensitivity (1), diarrhoea (1), flushing (1), renal function abnormal (1), hypertriglyceridaemia (3), hypercholesterodaemia (2), drug maladministration (1), dermatitis (2) and death (3).

With these data the association between abacavir (a reverse transcriptase inhibitor) and myocardial infarction should not be ruled out, and further studied.

Table 1. Age groups (in years)

Age group	30-39	40-49	50-59	>60
Number of cases	7	16	5	1

Table 2. Reporting countries

Country	USA	FRA	GBR	SPA	CAN	DEU
Number of cases	19	5	2	1	1	1

Signal from Dr Emilio Sanz, Spain.

Table 3. Case report summaries.

	Time interval (months)	Protease inhibitor therapy	Dechallenge	Rechallenge	Outcome
1	15	X			Recovered
3	4				U
4	11	X			Recovered with sequelae
5	1d	X	X		U
6	23	X			U
7	52d				U
8	45d		X		U
9	16				Died
10			X	X	U
11			X		U
12	12				Recovered with sequelae
13		X			Recovered with sequelae
14	8	X			Recovered with sequelae
15		X			U
16	2d	X			Died
17	9	X			U
18		X			U
19	19d	X	X		Recovered with sequelae
21	15		X		Recovered
22	23	X			Not recovered
23	10				Died
26		X			U
27	11	X			U
28		X			Not recovered
29		X			U
30		X			U
31	12	X			U
33		X			U
34	9	X			U

U: unknown
d: days

References:

1. DRUGDEX(R) Editorial Staff 02/2004. Several references pointed out to the associated risks of protease inhibitors and MI. In particular see: *Combination antiretroviral therapy and the risk of myocardial infarction. The Data Collection on Adverse Events of Anti-HIV Drugs (DAD) Study Group. N Engl J Med 2003; 349(21):1993-2003.*

2. No references to cardiovascular side effects on Martindale or PDR (2004) (Micromedex).

Signal from Dr Emilio Sanz, Spain.

Editorial comment:

Dr Jens Lundgren and his group at the HIV Programme in Copenhagen, Denmark, is currently working on this issue.

Since this assessment three additional cases have been reported from the USA: All patients were male and of 32, 41 and 53 years of age. Outcome and dechallenge/rechallenge data was not stated. Co-suspected drugs on these three reports included didanosine/indinavir/ritonavir, amprenavir/didanosine/lamivudine (concomitantly cidofovir) and delavirdine.

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 statistically 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 (C_x); and
- the total number of case reports with adverse reaction term Y (C_y); and
- the number of reports with the specific drug-ADR combination (C_{xy}); 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 C_x , C_y and C_{xy} values are, the narrower the confidence interval. The IC025 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 IC025 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.

For more information, please contact:

the Uppsala Monitoring Centre
Stora Torget 3
753 20 Uppsala
Sweden

E-mail: info@who-umc.org



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 pharmaceutical 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.



WHO Collaborating Centre
for International Drug Monitoring
Stora Torget 3, SE753 20 Uppsala, Sweden.
Tel +46 18 65 60 60. Fax +46 18 65 60 80.
E-mail: info@who-umc.org