Thérapie 2013 Mars-Avril; 68 (2): 69–76
DOI: 10.2515/therapie/2013016

Updating the French Method for the Causality Assessment of Adverse Drug Reactions

Cercle de Réflexion sur l'Imputabilité (CRI) : Yannick Arimone[1], Irène Bidault[2], Jean-Paul Dutertre[3], Marie Gérardin[4], Claire Guy[5], Françoise Haramburu[6], Dominique Hillaire-Buys[7], Carmine Meglio[8], Catherine Penfornis[9], Hélène Théophile[6] and Marie-Blanche Valnet-Rabier[10]

1 Cellule Plan de Gestion de risque, ANSM, Saint-Denis, France
2 Département de Pharmacovigilance, ANSM, Saint-Denis, France
3 Pharmacovigilance, Laboratoires SERB, Paris, France
4 Service de Pharmacologie clinique, CHU Nantes, France
5 Centre régional de Pharmacovigilance et de Renseignement sur le Médicament, CHU Saint-Étienne, France
6 Centre régional de Pharmacovigilance et de Renseignement sur le Médicament, CHU Bordeaux, France
7 Centre régional de Pharmacovigilance et de Renseignement sur le Médicament, CHU Montpellier, France
8 Pharmacovigilance, Laboratoire Lilly, Neuilly sur Seine, France
9 Global Pharmacovigilance & Epidemiology, Sanofi-Aventis Research & Development, Chilly-Mazarin, France
10 Centre régional de Pharmacovigilance et de Renseignement sur le Médicament, CHU Besançon, France

Text received October 25th, 2012; accepted January 7th, 2013

Keywords:
adverse drug reaction;
causality assessment;
algorithm;
drug safety

Abstract – The Imputability Working Group (CRI) updated the French drug reaction causality assessment method. This tripartite group is made up of staff from the French network of regional pharmacovigilance centres, pharmaceutical companies, and the French National Agency for the Safety of Medicines and Health Products (ANSM). After reviewing the strengths and weaknesses of the previous method, several ideas for improvement were proposed: a better-worded and more discriminating scale for certain chronological and semiological criteria, a larger scale for the intrinsic score (increased from 5 to 7 levels), a new bibliographical scale to differentiate between expected and unexpected adverse drug reactions, and a new informativeness scale.

Mots clés :
effets indésirables médicamenteux ;
imputabilité ;
algorithme ;
pharmacovigilance

Résumé – Réactualisation de la méthode française d'imputabilité des effets indésirables des médicaments. Un groupe tripartite, le Cercle de réflexion sur l'imputabilité, associant des pharmacovigilants du réseau français des centres régionaux de pharmacovigilance, de l'industrie pharmaceutique, et de l'Agence nationale de sécurité du médicament et des produits de santé (ANSM), a travaillé pour réactualiser la méthode française d'imputabilité. Après analyse des forces et faiblesses de cette méthode, plusieurs points d'amélioration sont proposés : une formulation plus précise et une cotation plus discriminante de certains critères chronologiques et sémiologiques, une distribution élargie du score d'imputabilité intrinsèque (augmenté de 5 à 7 niveaux), une nouvelle cotation bibliographique permettant de distinguer le caractère attendu/inattendu de l'effet et l'introduction d'un score d'informativité.

Abbreviations: see end of article.

1. Introduction

In pharmacovigilance, causality assessment consists of estimating the probability of a relationship between the intake of a drug and the occurrence of an adverse reaction. This is a specific analysis for a given case at a given point in time. Causality assessment is called imputability in France to avoid potential confusion with the legal concept of cause. The first imputability method[1] was published in 1978 and revisited in 1985 by Bégaud *et al.*[2] It is official and mandatory for cases arising from spontaneous reporting (see the French ministerial order of 28 April 2005 on good pharmacovigilance practice).[3] It is used by regional pharmacovigilance centres and pharmaceutical companies. This method has been discussed at national pharmacovigilance workshops, but has not been modified since it was last updated in 1985. It is recognized as a simple tool to assess the causal relationship between a drug and an adverse reaction and

- **More discriminating intrinsic imputability:**
  - o More precise definitions for chronological and semiological criteria
  - o Better separation of different situations to obtain a refined semiological score (with additional table row and column, introduction of a S0 score)
  - o More detailed description of special situations (withdrawal syndrome and interactions)
  - o New calculation method for the intrinsic imputability score expanded to 7 levels (I0 to I6)
  - o Intrinsic imputability score expressed on a graduated scale from 0 to 6 without any denominations (which, in the past led to confusion with other methods using the same adjectives)
- **New bibliographical scale:**
  - o Introduction of the B4 score for differentiation of the expectedness of an adverse drug reaction
  - o Deletion of the B0 score
- **Introduction of a new informativeness score**

Fig. 1. Summary.

standardizes the causality assessment process. However, the use and interpretation of this method have some limitations.[4] After the 20th Pharmacovigilance Workshop, a group was created in 2006 called the Imputability Working Group (CRI). This tripartite group is made up of staff from the French network of regional pharmacovigilance centres, pharmaceutical companies, and the French National Agency for the Safety of Medicines and Health Products (ANSM). The objectives of the CRI were to increase the imputability method's sensitivity and improve its reproducibility to reduce discrepancies when interpreting criteria between users.

During CRI working sessions, several areas for improvement were proposed: a better-worded and more discriminating scale for certain chronological and semiological criteria, a larger scale of intrinsic imputability levels (increased from 5 to 7 levels), a new bibliographical scale to differentiate between expected and unexpected adverse drug reactions, and the introduction of an informativeness score (figure 1). The revised and validated imputability method is reported here.[5]

2. Principles for using the method

- A valid pharmacovigilance case is defined by the presence of four items: a reporter, a patient (defined by his/her gender, age or age class, or initials), a drug, and an adverse reaction.
- Imputability and informativeness score should be determined independently for each drug.
- Assessment takes all components of the drug (active substance(s) and its metabolites, excipients, etc.) into account.
- For each case, imputability should be determined for all adverse reactions included within the same nosological entity.
- Imputability is determined at a precise time and may change over time (depending on any additional information available for the case and/or the drug).

3. Informativeness score

One of the difficulties in interpreting and using the final imputability score comes from the level of information from available data. For one case, levels of informativeness can be different for drugs with similar intrinsic imputability scores regardless of the information source. It became necessary to add an informativeness score to the imputability method that is independent of the imputability score, so that each suspect drug would have an additional discriminating item. As with the imputability score, this categorization is contextual and evolves over time. The objective of this score is to quickly evaluate the level of informativeness (NI) available for each drug.

Available information components (a and b) are defined as follows for each adverse reaction-drug pair:

a) the time of occurrence for adverse reactions compared with the drug exposure period;

b) information on continuing or discontinuing the drug or dose adjustment.

Informativeness is classified into three levels for each adverse reaction-drug pair, depending on available information.

NI 2: items *a* and *b* are specified.
NI 1: one of the items *a* or *b* is not specified.
NI 0: items *a* and *b* are not specified.