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Causality assessment: A brief insight into practices in pharmaceutical industry

Abstract

Healthcare industry is flooded with multitude of drugs, and the list is increasing day by day. Consumption of medications has enormously increased due to life style changes, having safer drugs is the need of the hour. Regulators and other authorities to have a check have put in stringent regulations and pharmacovigilance system in place. Eventhough there has been increase in adverse drug reactions (ADR) reporting in the last decade, causality assessment has been the greater challenge for academicians and even industry. Causality is crucial for risk benefit assessment, particularly when it involves post marketing safety signals. Pharmaceutical companies have put in efforts to have a standardized approach for causality assessment. This article will provide some insight into the approaches for causality assessment from a pharma industry perspective.

Key words: Adverse drug reactions, causality, pharmacovigilance

INTRODUCTION

There is a dramatic increase in number of molecules under development due to increased health-care need. The main focus of regulators is to scrutinize the market authorization holders for providing safer drugs to the society and this can be ensured only through a robust pharmacovigilance system in place.

In the last decade, there has been an increase in reporting of adverse events. However, establishment of a causal relationship between the drug and the adverse event is a challenge and carries utmost importance in the current scenario of emerging adverse events. In current medical practice in emerging countries, many health-care professionals (HCP) are still unaware of adverse drug reactions (ADR) reporting process or importance of causality assessment. A major cause of morbidity increased hospital admissions has been directly linked to ADRs.

Access this article online

Quick Response Code:

Website: www.picronline.org

DOI: 10.4103/2229-3485.120173

The causality assessment system proposed by the World Health Organization Collaborating Centre for International Drug Monitoring, the Uppsala Monitoring Center (WHO-UMC) and the Naranjo probability scale are the generally accepted and most widely used methods for causality assessment in clinical practice as they offer a simple methodology.

Many multinational pharmaceuticals have adopted a structured way of capturing the ADRs and its causality assessment, which is still lacking in academics and general practice. This article will focus on industry perspectives of causality assessment and a brief review of causality assessment.

REVIEW OF EXISTING CAUSALITY PRACTICES

An inherent problem in pharmacovigilance is that most case reports concern suspected ADR. Adverse reactions are rarely specific for the drug, diagnostic tests are usually absent and a re-challenge is rarely ethically justified. In practice, few adverse reactions are "certain" or "unlikely;"

most are somewhere in between these extremes, i.e., "possible" or "probable." In an attempt to solve this problem, many systems have been developed for a structured and harmonized assessment of causality.[1] None of these systems, however have been shown to produce a precise and reliable quantitative estimation of relationship likelihood. Nevertheless, causality assessment has become a common routine procedure in pharmacovigilance.

Few years ago, causality assessment was completely dependent on expert judgment (also known as global introspection,[2] unstructured clinical judgment,[3] striking case method,[4]) wherein, an individual expert or panel of experts would take a decision based on their expertise in the field of medicine.

However, with the increasing need of causality assessment and maintain the uniformity by decreasing the disagreement between the assessors there were a number of algorithms and tools developed to have a structured approach (e.g., pattern detection, decision tables, probabilities).

Few of the standards particised across the industry mentioned as below, WHO-UMC system,[5] was developed in consultation with the National Centers participating in the Program for International Drug Monitoring and is meant as a practical tool for the assessment of case reports. It is basically a combined assessment taking into account the clinical-pharmacological aspects of the case history and the quality of the documentation of the observation. This method gives guidance to the general arguments, which should be used to select one category over another.

The assessment criteria of the various categories are shown in a point-wise way as has been developed for practical training during the UMC Training courses. Causality terms include certain, probable/likely, possible, unlikely, conditional, and unassessable.

Naranjo algorithm,[6] was developed in 1991 by Naranjo *et al.*, from the University of Toronto and is often referred to as the Naranjo Scale. This scale was developed to help standardize assessment of causality for all ADR. The scale was also designed for use in controlled trials and registration studies of new medications, rather than in routine clinical practice. Nevertheless, it is simple to apply and widely used.

Questionnaire designed by Naranjo *et al.*, for determining the likelihood of whether an ADR (adverse drug reaction) is actually due to the drug rather than the result of other factors. Probability is assigned via a score termed definite, probable, possible or doubtful.

The Hill criteria,[7] otherwise known as Hill's criteria for causation, are a group of minimal conditions necessary to provide adequate evidence of a causal relationship between incidence and a consequence, established by the English epidemiologist Sir Austin Bradford Hill (1897-1991) in 1965. Criteria assesses causality from multiple information sources using the following parameters-strength of association, temporality, consistency, theoretical plausibility, coherence, specificity in the causes, dose response relationship, experimental evidence, analogy.

Structured methods of causality assessment have their own limitations.

Limitations of structured approaches to case causality assessments

- Repeatability — given the same information, different assessors should reach the same conclusions.
- Explicitness — the method should require the user to make explicit its state of information and to state its degree of uncertainty about each element of information.
- Explanatory capacity — from the information, the users must be able to explain how they reached their conclusions.
- Completeness — the user must be able to incorporate any fact, theory or opinion that can affect the assessment.
- Biological balancing — the probability that the suspect drug caused the Adverse Event (AE) must be weighed against the probability that an alternative candidate caused it.
- No *a priori* constraints-no score or specific weighting given before the assessment.

INDUSTRY PERSPECTIVE

Initially, investigators/sponsors were too cautious in their interpretation of "reasonable possibility." They submitted reports for events that were likely to be manifestations of disease, common, probably unrelated events or study endpoints. Food and drug administration (FDA) and European medical agency (EMA) received too many suspected unexpected adverse reactions reports for which there was no evidence of "relatedness." This necessitated regulators to push the pharma companies to have a validated system in place for causality assessment and outlined few guidelines and recommendations (e.g., methods for the assessment of individual cases guidance Council for International Organizations of Medical Sciences (CIOMS) VI (2005), guidance FDA (2010),[8] EMA guideline (2012)[9]).

RECOMMENDATIONS

- Binary yes/no causality (i.e., related/not related) for study investigators.

- Grades of causality (e.g., "possible," "probable," "definite") offer little practical advantage. Only "related" versus "unrelated" is needed for regulatory reporting requirements.
- Poor inter-rater agreement using terms such as "possible" or "probable."
- Investigator should complete a checklist of potential causes and events should be considered related if there is "a reasonable possibility of a causal relationship rather than if "a causal relationship cannot be ruled out."
- For regulatory reporting purposes, all spontaneous reports are considered suspected adverse reactions unless the reporters specifically state they believe the events to be unrelated.

"Case processing" is the name given in the industry to the activities that start with a fax or phone call from a patient, pharmacist or physician, through to the final, complete case report.

Usual process flow of case processing in an ADR is as follows,

HCP/non-HCP

Records all adverse events in a case record form including, assessment of seriousness and relatedness (causality).

Serious events — defined according to International Conference on Harmonization guidelines by the investigator to be medically significant and protocol-defined events of special interest.

Safety operations

- Assess expectedness, seriousness and relatedness.
- Company does not down grade the reporter's assessment.

Health authorities

- Life-threatening or fatal events (≤ 7 days).
- Other events (≤ 15 days).

A major challenge faced when processing individual cases, is to quickly identify the most informative reports, i.e., those providing compelling evidence of new ADR.

Spontaneously reported events are all considered causally "related" to the drug for initial triage purposes unless explicitly considered by the reporter to be unrelated. For adverse events submitted from trials an initial decision regarding relatedness is more important. Adverse event reports captured in the company drug safety database are heterogeneous in terms of the reporter's level of concern regarding a causal role of the drug.

Although a binary yes/no approach to causality assessment is convenient, and is needed for regulatory reporting purposes, such an approach does not necessarily reflect the process that occurs in clinical practice, where diagnoses are often made with degrees of certainty.

Few points are worth noting. First, the recommendation of a regulatory working group (CIOMS VI) to use a binary yes/no causality assessment; second, the concern expressed recently by the FDA about the number of adverse event reports from clinical trials assigned as "related" due to precaution rather than positive information to indicate a causal relationship.

The Naranjo algorithm was used at Roche between 2001 and 2009 to assist in the triage of certain types of case during case processing, but proved to be generally unhelpful and was subsequently withdrawn. The Hill criteria are widely used for causality association in pharmacoepidemiological studies and in aggregate reporting. With a robust training in place and having a standardized approach for causality assessment many pharma companies are focused on a robust pharmacovigilance platform.

Expressing causality in words is not without problems, and the challenge of communicating probability should not be underestimated — possible has many shades of meaning.

There is much to take into account when assessing a new safety signal, although the focus of each investigation depends on the drug-event pair in question. For example, in some instances, one or two case reports may provide compelling evidence of causality. In others, pre-clinical or epidemiological data may be the focus of attention.

It is important to remember that having decided that a causal relationship exists, simply adding a new adverse event to the product label is not enough. The prescriber and patient must also be informed about the probability and clinical importance of the event.

The utility of causality assessment as applied at the individual level or triggered by signal detection (population level) remains a matter of discussion for both industry and regulators.

CONCLUSIONS

In pharmaceutical industry, structured causality assessment methods for individual cases have been used to facilitate case processing rather than to reach definitive conclusions. Events are considered "related" or "not related" for the purpose of case processing and regulatory reporting.

Definitive decisions about causality (leading to risk management plan/label changes etc.), usually incorporate evidence from various sources. However, no single "one size fits all" approach exists as sometimes individual case reports provide compelling evidence of causality.

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How to cite this article: Naidu RP. Causality assessment: A brief insight into practices in pharmaceutical industry. Perspect Clin Res 2013;4:233-6.

Source of Support: Nil. **Conflict of Interest:** None declared.