

Lecture 04: Causality - Theory

1. Basic information

Author: Netherlands Pharmacovigilance Centre Lareb

Version date: 25 October 2018

Content: This hand-out describes causality assessment of ADRs and provides background information on the lecture 'Causality assessment - Theoretical background, by E. van Puijenbroek, The Netherlands. This lecture is part of the **WHO PV core curriculum for university teaching**. The outline of this core curriculum consists of 5 key aspects on pharmacovigilance. This lecture refers to key aspect 2, 3 and 4 (i.e. preventing, recognizing and managing ADRs).

Current subject

Text to lecture on 'Causality assessment – Theoretical Background', by E. van Puijenbroek, The Netherlands.

Learning objectives: Understand the concept of counterfactuals
Apply the role of the Bradford Hill criteria in causality assessment
Knowing the difference between extrinsic and intrinsic causality

Target audience: Medical, pharmacy, nursing students; end of Bachelor phase, start of Master phase

Requirements: Knowledge on pharmacology, pharmacotherapy

Additional methods: problem solving cases or real patients during internships, collecting information on specific ADRs and apply classification systems, identify risk factors.

Origin

Author: E. van Puijenbroek, The Netherlands Pharmacovigilance Centre Lareb, University of Groningen

Date: 2017

Aim: Lecture on Clinical pharmacology of ADRs in a 2-week pharmacovigilance course

Audience: Pharmacy students, 1st year Master phase

2. Lecture: Causality-Theory

Outline

1. Counterfactual theory
2. Bradford Hill criteria

Introduction (slide 1)

How sure can one be about the fact that an adverse event (which is an event that is not necessarily related to the use of a drug) is indeed caused by the use of a drug and thus should be called a true adverse drug reaction? By so called “causality assessment” the strength of a causal relationship between a drug and a clinical event that occurs in a patient can be assessed. Causality assessment may be needed for several reasons:

- In individual patient care, since everyone faces uncertainties in diagnosing ADRs. For future advice, it might be useful to know how certain the causal relationship of the ADR was in your patient.
- In addition, causality assessment is needed when when analyzing case series that may point to yet unknown ADRs. Examples are clinical research and pharmacovigilance’ signal detection.

Learning objectives (slide 2)

In this lecture, we will start by looking at the idea of Causality by using so-called counterfactuals. Subsequently we will focus on criteria that play a role in assessing the strength of the causal relationship in the individual patient. For this we will use the Bradford Hill criteria.

Outline (slide 3)

In this lecture we start with a brief explanation of what causality actually is, by looking at the counterfactual theory. Then we will a more detailed look at factors that play a role in assessing the causality in an individual patient using the “Bradford Hill criteria” We will end this lecture with examples of questions you may expect at the exam

Questions (slide 4 & 5)

To discuss. Of course it is important to annotate the strength of the relationship between drug en adverse event, but it may be more important to mention the reasons underpinning your judgement as well. It will rarely be possible to exactly determine the strength of the association between drug and event. There will always be subjective elements in the assessment.

2.1 Counterfactual Theory

Counterfactual theory (slide 6)

A way to express the causal relationship between events is the use of counterfactuals. The idea of counterfactual theories of causation is that the causal relationship between these events can be expressed by so called “counterfactual conditionals”. An example is for instance: “When B occurs after X and B does not occur without X, then X is considered to be the cause of B”

- Someone entered his house (B) because the door was open (X) or
- Because he uses this drug (X), he got an Adverse Drug reaction (B)

In other words: “If X had not occurred, B would not have occurred”. This is a theoretical concept, but let’s see how we can use these concept in the case of adverse drug reactions. What do these “counterfactual conditionals” look like in case of adverse drug reactions?

Counterfactual theory (slide 7)

In the case of a suspected ADR with drug X, we cannot be a 100% sure about the causal relationship. In case there would be a causal relationship, we can say that:

- When he uses this drug (X), he got a clinical event (B) but
- When he does not use this drug (X), the event (B) would not have occurred

Counterfactual theory (slide 8)

We could only be sure that when the patient would not have used the drug when we could draw back time, keep everything exactly the same, but do not give the drug and see if the ADR does not occur. Of course this is not possible.

Counterfactual theory (slide 9)

The counterfactual theory describes what we consider to be a causal relationship. However, when we apply this theory on the assessment of the causal relationship of an adverse drug reaction, we see that it will never be possible to assess the existence of a causal relationship beyond any doubt.

So how did we solve this problem?

- Study setting: use control groups
- Assessment of individual cases: causality models

The epidemiological approach (slide 10)

In the setting of a study, like in clinical trials, we design control groups that resemble strongly the intervention group. In trials we can determine a causal relationship if there is a significant difference between well-chosen control groups.

Exchangeability of groups should be large; both groups should be comparable, except of course for the use of the drug (X). In other words:

- Patients (using X) → occurrence of B, given use of X
- Patients (no X) → occurrence of B, given no use of X

When both groups are “exchangeable”, and B differs between both groups, we state the B has a causal relationship with X. Size of both groups should be very large when a small relationship exists and conclusive proof of cause-effect relationship is often not possible

Conclusive epidemiological evidence? (slide 11)

Based on epidemiological studies, information about “chances” (Risk) for events to occur in groups of patients may be available. In medical practice methods to assess individual risks are also needed. In other words: I have a patient with specific symptoms, what is the chance that I’m dealing with an adverse drug reaction.

2.2 Hill’s criteria

Outline (slide 12)

Whereas in epidemiological studies the use of large groups are a proxy to apply the counterfactual theory, this is not possible in situation where we only have one single case. An example is the clinical situation where a patient asks you if the skin reaction he or she experienced is due to an adverse drug reaction or not? Can I tell something about the strength of the causal relationship in an individual patient? What kind of information may be helpful?

The basis to assess the strength of the causal relationship in this situation was led by sit Bradford Hill.

Bradford Hill (slide 13)

The English epidemiologist and statistician sir Austin Bradford Hill is widely known for pioneering the "Bradford Hill" criteria for determining a causal association.^{[2][3]} In the '60 Sir Bradford Hill composed a set of 9 criteria that could help to determine a causal relationship of a certain association, for instance a drug – adverse event association. These criteria form a basis for clinical reasoning and causality assessment. Note that not all criteria can be applied in every single situation. The majority of the causality models we apply today in pharmacovigilance largely depend on the criteria formulated by Bradford Hill.

Overview Bradford Hill criteria (slide 14)

In the following slides we will discuss these criteria and see how they can be applied for determining the causal relationship between a drug and a clinical event. Later on in the presentation we will discuss two models for causality assessment in more detail and see how they should be applied in practice.

1 *Strength of the evidence (slide 15)*

How strong is the association between the cause (drug) and the effect (adverse event)? What is the additional risk for the specific outcome after taking a drug? This can be illustrated with the increase of the relative risk on venous thrombosis while taking an oral contraceptive. The risk is relatively low, but more profound in third generation pills (third generation type progestogen) compared to non-use and to second generation pills. Note: in first generation pills the amount of estrogen was higher than in 2nd and 3rd generation pills.

For the individual young woman who recently started using an oral contraceptive and who suffered from an acute onset of shortness of breath, this means that taking a 1st or 3rd generation oral contraceptive will increase the a priori chance for the existence of and pulmonary embolism versus non-use or the use of a 2nd oral contraceptive. Although of course in this situation the absolute chance is still low.

2 *Order in time (slide 16)*

The order should be: exposure to the drug → adverse effect → treatment → resolution. With exposure to drug X being the cause. It is obvious that when a clinical event precedes the use of the

drug, it won't be causally related. In patients with polypharmacy, the recollecting the exact timing of events and start dates of drugs can be challenging.

Time to onset (slide 17)

Not only the order of time is important. Also the time to onset can be very characteristic. The importance of knowledge of the timing of the event is illustrated by the example of intestinal adverse events following an oral rotavirus vaccination. Adverse events following oral vaccination are expected in the first few days after administration. For diarrhea and gastro-enteritis this was the case in the study of Van Holle et al. Very specifically, intestinal intussusception (or bowel invagination) was seen with a time-to-onset a few days later.

Intussusception (slide 18)

This applies with the development of such a condition, in which part of the bowel folds into the next section; symptoms include abdominal pain, vomiting and bloody stool. This condition may occur in children and mostly the exact cause is unknown, although infections and malformations may pose an additional risk. Keep in mind that this specific rotavirus vaccination is no longer available due to this risk of intussusception that other rotavirus vaccines do not have.

Time to onset (slide 19)

Another example of specific timing is an urticarial rash which is typical for type I (IgE mediated, immediate) allergic reaction, whereas other skin rashes occur later on and after less specific timing. The development of malignancies takes at least months to years before they are detected.

3 *Consistency (slide 20)*

Consistency refers to the situation that multiple epidemiologic studies carried out in different situation and that may vary for instance in respect to locations, populations, and methods applied show a consistent finding. Even in a single study, the association may be present because of threats to internal validity. For this reason it is important to find similar findings in different settings and using different methods.

For the individual patient this means that once a possible association between drug and adverse reaction has been established in various studies and settings, the "a priori chance" for the presence of a true adverse drug reaction will be increased.

The concept of consistency has shown to be of extreme importance in pharmacovigilance, as is illustrated by the next example.

Consistency Thalidomide (slide 21)

At the beginning of the historic disaster of thalidomide and birth defect (limb malformations), one observer was asking other doctors if they had seen similar abnormalities in women taking this drug. This slide shows the first publication in medical literature in which the possible relation between the use of thalidomide and phocomelia has been mentioned. Once several findings, linking the use of thalidomide with the occurrence of these birth defect were published, people realised that the use of this drug was indeed linked with the malformation.

The importance of combining information from different settings led to the establishment of pharmacovigilance centres worldwide, whose main task was to analyse and combine this type of information in the form of reports from healthcare professionals (and later also from patients).

Consistency Meta analyses (slide 22)

The importance of consistency is also shown when assessing meta-analyses. This slide shows a forest plot, a graphical representation of estimated results from multiple scientific studies. These studies

address the same question. This example shows the association between carbamazepine causing serious skin reactions and HLA-A-3101 genetic variation. The Odds ratios for all investigated skin reactions indicate that this specific HLA type is more likely associated with carbamazepine causing these reactions. So in this case the consistent pattern in the forest plot support the fact the carbamazepine is indeed associated with these severe reactions.

4 *Plausibility (slide 23)*

The effect must have a biologic plausibility. This implies that the findings from epidemiological studies are in line with the assumed biological mechanism. The knowledge of biological pathways by which mechanism can be explained. However, since multiple mechanism may be involved, it may be difficult to demonstrating the biological plausibility.

For the individual patient this means that once a possible association between drug and adverse reaction is biologically plausible, the “a priori chance” for the presence of a true adverse drug reaction will be increased.

Plausibility Risk Management Plan (slide 24)

The concept of biological plausibility plays an important role in pharmacovigilance. In Risk Management Plans (RMPs), the pharmaceutical industry (Marketing Authorisation Holders) and regulatory authorities summarize what adverse drug reactions can be expected and how these should be managed. Of course, not all biologic possibilities are known at a certain moment. In future, more knowledge may appear.

5 *Specificity (slide 25)*

Some ADRs are very specific for certain drugs. In rare cases, there may be a specific mechanism in place that is responsible for a typical reaction. However, specificity is not a criterion that is often used in the assessment of the causal relationship, simply because of its rarity.

Also in this case it means that for the individual patient a specific association between drug and adverse reaction, the “a priori chance” for the presence of a true adverse drug reaction will be increased.

Chloroquine induced maculopathy (slide 26)

One example is chloroquine induced maculopathy, the so called ‘bull’s eye’. By binding to melanin pigment in the retinal epithelium, chloroquine and hydroxychloroquine may cause damage to the retina. This condition is mainly associated with long-term use of these specific drugs.

Nicolau syndrome (slide 27)

Nicolau syndrome also is a specific reaction; in this case to intramuscular administered diclofenac (and a few other drugs). The condition is characterized by tissue necrosis due to ischemia.

Amiodarone-induced skin discoloration (slide 28)

Long-term therapy of amiodarone can cause a typical blue-grey skin discoloration sun exposed skin area, based on skin hyperpigmentation. In dermal cells, yellow-brown deposits of lipofuscin aggregates with amiodarone can be found.

Specificity of the association (slide 29)

Although rare, when present, a specific reaction is a strong predictor of the existence of a causal relationship. This table gives you an overview of the mechanisms that are responsible for the occurrence of these specific reactions. Sometimes, the culprit drug can be found at the site of the adverse reactions, as is shown in examples in the table: stone formation, crystal formation, extravasation of drug, photosensitivity and sepsis with live-vaccine induced infection.

6 *Biological gradient (slide 30)*

If a reaction is more severe with higher dose of the drug, there is a pharmacological plausibility. In case dose dependency is present in a patient, this is a strong predictor for the existence of a causal relationship.

Dose-response curve type A reactions (slide 31)

Dose-response curves reflect the threshold dose of a drug for its therapeutic effect as well as for adverse drug effects. The higher the dose, the bigger the chance of developing an adverse drug reaction (type A reactions). This effect is present for the majority of adverse drug reactions.

Dose-response curve type B reactions (slide 32)

However, also in the lowest dose range, a similar principle can be found: with very low doses of a drug in a susceptible patient a reaction does not have to appear. This mechanism is present in type B (Bizarre) reactions, which usually are rare and seems not to seem be dose dependent at first glance. This also holds for allergic reactions. Those of you who suffer from hay fever –which is a type I IgE mediated allergic reaction – will realize that, depending on the pollen count in the air, symptoms may vary. So in low dosage, also for type B reaction, dose dependency is present. However, at therapeutic doses in drug use, this effect is not seen, and a susceptible patient will always develop the allergic reaction.

7 *Coherence (slide 33 and 34)*

The interpretation of the cause and effect of a suspected adverse drug reaction should not conflict with generally known facts of nature and biology. This aspect is closely related to plausibility and will not be discussed in detail since its added value for causality assessment is limited.

8 *Experiment (slide 35)*

Dechallenge and rechallenge experiments are strong predictors in the assessment of causality. In dechallenge, symptoms subside and in rechallenge, symptoms reappear when the patient is exposed to the drug once again. In daily practice however, these experiments may be hampered by medical interventions, such as additional treatment of the symptoms, or may not be ethical by reintroducing a life-threatening condition.

Patch testing (slide 36)

In drug allergy, patch testing can be carried out to find out which drug, allergen or component is the culprit substance causing the allergic reaction. By means of this method it can be determined if a specific substance causes allergic inflammation of a patient's skin. This is caused by a delayed-type allergic reaction (type IV) in a patient. When the patches are removed after 2-4 days, the causative agents causing the delayed type reaction can easily be identified. Patch testing is one of the “experiments” that have a strong predictive value for the existence of cell mediated allergic reaction to the use of drugs.

9 *Analogy (slide 37)*

If one drug of a chemical class can cause a certain reaction, it is reasonable that similar drugs may act likewise. In case patients use related drugs that have proven to cause a certain adverse drug reaction, this increases the likelihood that patients suffer from and adverse drug reaction indeed.

Analogy (slide 38)

At The Netherlands Pharmacovigilance Centre Lareb, we detected that mercaptopurine could cause photosensitivity reactions. A few years later, after receiving ADR reports of azathioprine and photosensitivity reactions, it was concluded that both drugs have similar properties for causing

photosensitivity. Mercaptopurine is one of the metabolites of azathioprine, so the existence of a true adverse drug reaction is likely in this case.

Overview (slide 39)

So far we discussed nine different criteria that may contribute in the assessment of the causal relationship between the use of the drug and the suspected adverse drug reaction. Please note that some of these criteria tell us something about the prior chance that we are dealing with an adverse drug reaction. These are called “extrinsic factors”, since they tell us something about the existence of a relationship in the population-how well known is this ADR? Others tell us something about the clinical presentation in this specific patient (also called intrinsic factors). You might have noticed that plausibility has both extrinsic and intrinsic values: what is known about the mechanism and what patient-related factors affect this mechanism (for example: genetic variability in drug metabolism alters blood levels).

Extrinsic factors are

- Strength
- Consistency
- Plausibility
- Specificity
- Coherence
- Analogy

Intrinsic factors are

- Temporality
- Plausibility
- Biological gradient
- Experiment

We will see the use of various intrinsic and extrinsic factors also in various causality models, which will be discussed in the next section of this presentation

Quote Bradford Hill (slide 40)

The aforementioned criteria provide guidance to the assessment of the causal relationship. However, as also suggested by this quote of Bradford Hill, it is not needed that all these criteria are present. Moreover, some of them may have a greater impact than others and their contribution may also differ for various situations. You may imagine that the assessment of an allergic reaction can differ from the assessment of a hepatic reaction. For this reason, several dedicated models that can be used to assess the strength of the causal relationship have been developed over time.

Exam question (slide 43)

This statement is correct

Exam question (slide 43)

The correct answer is a)

Literature (slide 45)

Optional literature

1. Hill, Austin Bradford (1965). "The Environment and Disease: Association or Causation?". *Proceedings of the Royal Society of Medicine*. 58 (5): 295–300.. PMID 14283879.

2. Höfler M (2005). "The Bradford Hill considerations on causality: a counterfactual perspective?". *Emerging themes in epidemiology*. 2 (1): 11. doi:10.1186/1742-7622-2-11. PMID 16269083.

2.5 Literature used in this lecture:

1. Hill, Austin Bradford (1965). "The Environment and Disease: Association or Causation?". *Proceedings of the Royal Society of Medicine*. 58 (5): 295–300.. PMID 14283879.
2. Rotavirus vaccines. WHO position paper- January 2013. Pmid 23424730
3. Van Holle L, Zeinoun Z, Bauchau V, Verstraeten T. Using time to onset for detecting safety signals in spontaneous reports of adverse events following immunization: a proof of concept study. *PEDS* 2012;21(6):603-10
4. Nischal KC, Basavaraj et al. Nicolau syndrome: an iatrogenic cutaneous necrosis. *J Cut Aest Surg* 2009 2(2):92-95
5. Jaworski K, Walecka I, Rudnicka L, Gnatowski M, Kosior DA. Cutaneous Adverse Reactions of Amiodarone. *Medical Science Monitor : International Medical Journal of Experimental and Clinical Research*. 2014;20:2369-2372. doi:10.12659/MSM.890881.