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Causal Association in Pharmacovigilance and Pharmacoepidemiology

Thoughts on the Application of the Austin Bradford-Hill Criteria

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Abstract

The methods used for the evaluation of drug safety signals (including major signals leading to withdrawal of products from the market) are inconsistent and sometimes of poor quality. While the assessment of the safety of medicines needs to consider specific issues such as drug interactions and variation in compliance, the general principles, which are used to study environmental hazards, can be applied for this purpose. The criteria proposed by Sir Austin Bradford-Hill more than 35 years ago for attributing disease causation to environmental factors have been used widely in epidemiology, are applicable to pharmacovigilance and pharmacoepidemiology.

The Austin Bradford-Hill criteria include strength, consistency, specificity, temporality, biological gradient, plausibility, coherence, experimental evidence and analogy. The paper reviews each of these criteria with emphasis on pharmacovigilance and pharmacoepidemiology and with some examples. The application of the Austin Bradford-Hill criteria to the evaluation of causal association in pharmacovigilance and pharmacoepidemiology is very useful. However, it requires understanding of the limitations of the data, such as, under-reporting, poor quality of information from third parties and misclassification. Further work is required to develop strategies to handle these limitations.

Pharmacovigilance involves the monitoring, detection, evaluation and responding to drug safety hazards in humans during premarketing drug development and postmarketing. Drug safety signals or hypotheses are generated from several sources, including spontaneous reports of suspected adverse reactions, published case reports, clinical pharmacology, clinical trials and pharmacoepidemiological studies. Pharmacoepidemiology has been defined by Strom as the study of the use and effects of drugs in large numbers of people.[1] A slightly different definition is the application of epidemiological methods and concepts to study the uses and effects of medicines in large populations. Drug safety signals also are generated in biological models and animal studies. In an ideal world all generated signals would be evaluated and investigated further if necessary. Unfortunately this happens infrequently and usually in a limited way. Regulatory and clinical decisions have to be made on the data available at the time of evaluation. In 1998, the Council for International Organizations

of Medical Sciences (CIOMS) IV Working Group raised concerns regarding the limitations and inconsistencies of safety evaluations by regulatory authorities in respect of important drug safety issues such as product withdrawals.[2] The CIOMS IV report provided pragmatic yet comprehensive and useful guidelines for safety evaluation. Together with earlier initiatives,[2] the CIOMS IV report provide a good foundation to build on to improve safety evaluation, but the field requires further methodology and policy research and audit.

While the safety of medicines must consider specific issues such as variation in compliance and drug interactions, the general principles that are used to study environmental hazards are applicable with some modifications. One of the most important papers published in the 20th century with thoughts on the epidemiological basis of disease causation was a summary of a lecture given by Sir Austin Bradford-Hill (who was then Emeritus Professor of Statistics at the University of London, England) entitled; 'The Environment and Disease: Association or Causation' in 1965.[3] This lecture was delivered to the Section of Occupational Medicine at the Royal Society of Medicine. In the introduction, he asked two simple questions, 'How in the first place do we detect the relationship between sickness, injury and conditions of work? How do we determine what is a physical, chemical and psychological hazard of occupation, and in particular those that are rare and not easily recognised'. Sir Austin Bradford-Hill described 'aspects' of an association, which need to be considered before deciding that the most likely interpretation of its causation (see table I).

These aspects (table I), commonly referred to as the 'Austin Bradford-Hill criteria for causal association', have been used by epidemiologists and others when addressing causation of disease in a broad range of situations.[4] In his lecture, Sir Austin Bradford-Hill described strengths and weaknesses of each of these aspects with regard to its contribution to an inference of causation. These criteria have been used to interpret evidence from pharmacoepidemiological studies.[1] In the broader discipline of pharmacovigilance, the consideration of these criteria, with any modifications dictated by the nature of the data, can be very helpful in the interpretation of evidence from various sources at different levels. This paper describes thoughts on the application of Sir Austin Bradford-Hill's criteria to the evaluation of pharmacovigilance data with some examples.

Table I. The Austin Bradford-Hill criteria

Strength
Consistency
Specificity
Temporality
Biological gradient
Plausibility
Coherence
Experimental evidence
Analogy

1. Strength of Associations

Sir Austin Bradford-Hill stated that strong associations are more likely to be causal than weak associations. Weak associations are more likely to be explained by unrelated biases. For example, the association between smoking and lung cancer is so strong (studies show relative risks ranging between 10 and 30) that even if some biases were operating a shift of the association to non-causal is unlikely.[1] In epidemiology, a relative risk of less than two is considered to indicate a weak association.[1] This is one of the major problems of pharmacoepidemiology; because it is rare to find high relative risks (more than two) for adverse drug reactions (ADRs) – particularly serious ADRs – with marketed medicines compared with placebo or to other products. Medicines associated with a high incidence of serious ADRs would have been considered too toxic to be marketed.

With regard to pharmacovigilance, to enhance conventional signal generation methods, new approaches have been proposed such as proportional reporting rates (PRR)[5] and Bayesian confidence propagation neural network (BCPNN).[6] In essence, these methods compare the proportion of a

particular event reported for a drug with the whole database (which includes all the other products monitored by the organisation). High PRR or information component (IC) in BCPNN suggest that an event has been reported more frequently with a product which may indicate a safety signal. While higher PRRs and ICs do not indicate a higher likelihood of causality[5] they suggest stronger signals. Sir Austin Bradford-Hill's strength criterion can be applied in signal generation in pharmacovigilance. For example, in a recent study using the WHO database of spontaneous reports of ADRs, BCPNN was used to examine strength of the signals relating to heart muscle disorders with antipsychotic drugs.[7] Clozapine, an antipsychotic which had been previously reported to have been associated with heart muscle disorders, had a higher IC than lithium, a drug not known to be associated with such disorders. This example demonstrates the feasibility of applying the strength criterion to the quantitative methods for signal generation in pharmacovigilance.

2. Consistency of Findings

Sir Austin Bradford-Hill stated that repeated observations of an association in different populations under different circumstances provide additional support for a causal association. However, he cautioned that lack of consistency does not rule out a causal association, because some effects may be produced by the causes only in certain circumstances.

Because of the low relative risks of ADRs generally detected in pharmacovigilance and pharmacoepidemiological studies, the consistency of findings in different populations is highly important. For example, in studies conducted to examine the association between the use of the so-called 'third generation' oral contraceptives (gestodene and desogestrel) and deep vein thrombosis, while the strength of the association in some of the studies may have been weak by conventional epidemiological standards (low relative risk),[7] the consistency of the finding of a higher risk among users of the 'third generation' oral contraceptives in different populations utilising different methods supports an inference of causation

With regard to pharmacovigilance findings, reporting of a particular event in different populations is supportive of a true association. An example is the association between the antiepileptic product, lamotrigine, and serious skin reactions (Stevens-Johnson syndrome and toxic epidermal necrolysis) was strengthened by the fact that spontaneous reports were sent both from hospital and the community in several countries and that cases were reported in clinical trials,[8] and in a prescription-event monitoring (PEM) study.[9]

3. Specificity of the Association

Sir Austin Bradford-Hill stated that a cause leads to a single effect not multiple effects, but cautioned that although the concept of specificity is sometimes helpful, it could be misleading.

In pharmacovigilance specificity is important because drugs cause ADRs by specific mechanisms which may or may not be known at the time of the enquiry. Associations between the use of some drugs and an increase in the incidence of cancer have been reported e.g. prolonged use of hormone replacement therapy and slight increase in the incidence breast cancer.[10] True associations are specific, and in most circumstances it is not plausible that a drug is associated with an increase in developing multiple cancers. In the 1990s, a controversy was raised by a suggestion of an association between the use of intramuscular vitamin K in neonates and childhood cancer.[11] It is difficult to think of a mechanism by which a single injection can lead to an increase in the likelihood of developing several cancers in childhood. Subsequent studies were more focused in studying the association between injectable vitamin K in neonates and specific cancers, e.g. acute lymphoblastic leukaemia.[12] Discussion of the association between vitamin K and cancer is beyond the scope of this paper, but the example serves to demonstrate the need for specificity when considering a causal association in pharmacoepidemiology and pharmacovigilance.

4. Temporality

Sir Austin Bradford-Hill states that there is necessity that cause precedes effect in time. This is very important in pharmacovigilance. Most ADRs fall into what is conventionally described as 'type A' reactions, which are pharmacologically related to the drug, predictable, and usually dose related. Such ADRs occur in patterns based on relation to exposure, the pharmacological characteristics of the drug and host responses. Thus, a consistent pattern with regard to temporal relationship is very important in assessing the causal relationship between drug exposure and an adverse event or a cluster of events. Conversely, whilst an inconsistent pattern does not exclude a causal relationship, one should be suspicious of a possible causal relationship in such cases.

5. The Biological Gradient

Sir Austin Bradford-Hill stated that the biological gradient as demonstrated by a dose response curve is well known in epidemiology. It has been demonstrated in numerous studies that the number of cigarettes smoked and the number of years of smoking are directly related to the development of major smoking-related diseases (cancer of the lung and cardiovascular diseases).[1] However, care should be taken because biological gradient sometimes can be misleading. For example, while it is well known that excessive drinking of alcohol is associated with detrimental dose-related effects, drinking small amounts of alcohol can be protective.[13]

In pharmacovigilance a causal association is supported when an ADR occurs in a dose-dependent manner, or from cumulative exposure over a prolonged period of time. There are many examples when causal association was supported by plausible dose relationships such as the estrogen content of the combined oral contraceptive pills and deep vein thrombosis[14] and the systemic effects of nasal and inhaled corticosteroids.[15]

6. Plausibility of the Association

Sir Austin Bradford-Hill stated that biological plausibility of a hypothesis is another aspect to be considered for causal inference. He added that plausibility is an important concern which may be difficult to judge. In pharmacovigilance plausibility is easy when the mechanism is known, as in the case of nonsteroidal anti-inflammatory drugs and gastrointestinal bleeding.[16] However, it is difficult when the mechanism is unknown, in such situations ADRs may not be detected readily, an example is the delay in the recognition of the association between the use of practolol and the oculomucocutaneous syndrome.[17]

7. Coherence

Sir Austin Bradford-Hill defined coherence as the cause-and-effect interpretation whose data should not seriously conflict with generally known facts of the natural history and biology of a disease. The principle of coherence is useful in pharmacovigilance and pharmacoepidemiology. For example, the proposed possible association between a single intramuscular injection of vitamin K, the neonatal period and childhood cancers lacked coherence with the understanding at the time of the pathogenesis of cancer.[11] However, one has to be careful to ensure keeping an open mind regarding associations which are not coherent with contemporary knowledge.

8. Experimental Evidence

Experimental evidence as a supporter for causal inference is self-evident. Studies in biological models as well as animal and human experiments all lend support to signals raised by pharmacovigilance. In fact sometimes it necessary to conduct studies to better understand signals generated in pharmacovigilance and pharmacoepidemiology. This should happen more frequently.

9. Analogy

Sir Austin Bradford-Hill said that inventive scientists could find analogies everywhere. An ana-

logy finds a source of more elaborate hypothesis about an association under study. As elsewhere in biomedical sciences analogies can guide or mislead.

In pharmacovigilance analogies are frequently used to support assertions that the safety profile of a particular product is similar to others in the same therapeutic class. For example while cough has been reported in 5 to 20% of patients who take ACE inhibitors, e.g. captopril, the association between cough and angiotensin II receptor antagonists, e.g. losartan, has no pharmacological plausibility.[16,18] Therefore, in evaluating reports of cough with an angiotensin II antagonist, an analogy with the other angiotensin II antagonists can be proposed based on the pharmacological actions of the group. Similarly, the analogy between bupropion, an antidepressant which is also used to aid smoking cessation, and tricyclic antidepressants with regard to the risk of seizure is appropriate because all these products are associated with a risk of convulsions in patients with previous history of convulsions.[19,20]

10. Conclusion

To conclude, the application of Austin Bradford-Hill criteria for evaluating causal associations in pharmacovigilance as well as pharmacoepidemiology is very useful. However, the application requires understanding of the general characteristics of pharmacovigilance data, e.g. under-reporting, misclassification and poor quality of information from third parties. Further work is required to propose ways to handle such limitations.

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