Determination of Causation

A major component of the evaluation of reports of suspected adverse drug reactions, or events in a clinical trial, can be a judgment about the degree to which any reported event is, in fact, causally associated with the suspected, or investigational drug. In reality, a particular event is associated or is not associated with a particular drug, but the current state of information almost never allows a definitive determination of this dichotomy. (Jones 1994)

The analysis of causality and association in adverse drug events has not changed in the last 20 years. Riddell (1983) describes the "ways and means" of confirming or denying the possibility of an ADR which constitute a validation process that removes suspected cases from the merely anecdotal category. They are:

> 1. Temporal eligibility - drug must be administered at some interval of time before the reaction occurs.
>
> 2. Latent period - There is an interval from the time at whcih a drug is first administered to the beginning of the ADR.
>
> 3. Exclusion - are any other drugs or existing conditions responsible. This method is not applicable in all cases of possible ADR, either because of insufficient data or because of simultaneous eligibility of more than one drug.
>
> 4. De-challenge - condition improves on discontinuation of the drug, and

5. Re-challenge - condition reoccurs upon re-exposure to the drug (usually not

deliberately, since a suspicion of an association with an adverse event would preclude intentional re-exposure of a patient to the same adverse event.

6. Singularity of the drug - Is there something unique about the adverse reaction experience that is not consistent with any other drug taken or any existing disease condition.

7. Pattern - ADR been described in the literature with this drug or another in the same pharmacologic class, or it may refer to a morphologic pattern in a target organ that suggests an association with a particular drug or group of drugs. (Prior history with Hypervitaminosis A provides a literature precedent, a biological plausibility).

8. Drug Identification (qualitative or quantitative) - a major utility in overdose cases.

Hill Criteria for Causation

•1. Strength of association
•2. Consistency of results
•3. Specificity
•4. Temporal relationship
•5. Dose response
•6. Biologic plausibility
•7. Biologic coherence
•8. Experimentation
•9. Analogy

Causality assessments were usually expressed in terms of a qualitative probability scale, for example "definite" vs. "probably" vs. "possible" vs. "doubtful" vs. "Unrelated." (Hutchnson1989)

Hill Criteria – Expanded Discussion
1. Strength of Association

• **A strong association gives support to a causal hypothesis**

• **A weak association requires other information but can be equally as important**

2. Consistency of Results
- **Repeated findings in different populations and different settings**

3. Specificity
- **Strengthens confidence in association.**

- **Lack of specificity does not rule out causation**

4. Temporal Relationship
- **Required: exposure most come before disease**

5. Dose Response
- **Increased dose = increased risk**
- **Holds for drugs and vaccines (doses)**

6. Biological Plausibility
- **Known mechanism not required.**
  - **Cigarettes and lung cancer**
  - **Asbestos and lung cancer**
  - **Fen-Phen and valvular heart disease and PPH**

7. Biological Coherence
- **Does not conflict with what is known**

8. Experimentation
- **RCT is close to experimentation.**
- **Removal or reduction of exposure reduces disease.**
- **Challenge – dechallenge - rechallenge**

9. Analogy
- **Similarities with other like exposure**

- Aminorex and PPH

- Ergot drugs and VHD

• **Learn from past mistakes**

Algorythm-Based

• **Temporal relatedness**

• **Known or reported AE of Medication**

• **Presence of Concurrent Illnesses or medications which could present similarly**

• **Challenge – Dechallenge - Rechallenge**

Submission Of ADR Reports

ADR reports often paint an incomplete picture as the cases which are filed each year represent only a fraction of actual cases. According to the UK MCA only 10-15% of serious ADRs are ever reported. A FDA MedWatch Continuing Education article (Goldman et al 1996)describes significant underreporting in the United States. He cited estimates that rarely more than 10% of serious ADRs, and 204% of non-serious reactions are reported to the British spontaneous reporting program. A similar estimate is that FDA receives direct reports oless than 10% of suspected serious ADRs This means that cases spontaneously reported to any surveillance program, which comprise the numerator, generally represent only a small portion of the number that have actually occurred. The effect of underreporting can be somewhat lessened if submitted reports, irrespective of number, are of high quality.

Under regulations a pharmaceutical company must submit all ADR reports to the FDA

periodically (at least annually) or on an expedited basis within 15 days of receipt. The FDA, on January 5th 1998, sent a warning letter to Hoffman-LaRoche (New Jersey) for failing to submit a number of adverse drug experience reports that were both serious and unexpected, within 15 working days as required by regulations (21 CFR 314.80 (c)(1)) as recently as October 1997 (with some dating back to 1989)(Scrip 1998). The letter documented, among others, two ADR reports for Accutane which were received by the manufacturers on 9/04/91 and 7/24/91. Both reports were not received by the FDA until 10/8/97 (FDA/Middelkoop personal communication). In one case, for Tigason, the company reported the adverse drug event almost 11 years after receiving the information. Thus, although regulations require it, sometimes even the companies do not report in a timely basis, if at all. (Middelkoop, 2000)

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