Making Sense of Biostatistics: Assessing Drug Safety

By J. Rick Turner

Assessing a drug’s safety, both during preapproval studies and during postmarketing surveillance once the drug is being prescribed for patients, is of fundamental importance. No drug is immune to the possibility of side effects; if we want to reap the benefits of pharmaceutical therapy, we have to accept and address the risks associated with it. This requirement leads to the concept of the benefit:risk balance of a drug. For a drug to be approved by a regulatory agency, an investigational drug must show a favorable benefit:risk balance at the public health level. For an approved drug to be prescribed to an individual patient, the physician and patient must decide that the likely benefits of prescribing the drug to this particular patient outweigh the risks. While previous columns have addressed evaluation of efficacy, this column focuses on safety assessments.

The use of the words “safety” and “risk” highlights a philosophical challenge in this field. The discipline of drug safety does not assess the safety of a drug per se, but instead assesses the opposite – harm – done by the drug. In nonclinical studies, many aspects of a drug’s potential toxicity are investigated, and relatively less evidence of drug toxicity is considered as relatively greater evidence of drug safety (see Durham and Turner, 2008). In preapproval trials, the smaller the number of adverse events, the safer the drug is considered to be. The same logic holds for adverse drug reactions once the drug has been marketed. We could clarify what we are doing by using the term “drug harm” instead of “drug safety,” but this option does not seem a wise move: As Turner and Durham (2009, p. 139) observed, “The alternative term ‘drug harm’ may bring additional emotional fuel to situations that already have more than enough, especially since the term ‘drug safety’ is functionally synonymous.” Therefore, we will continue to use the term “drug safety.” Also, since a drug’s safety can only be meaningfully assessed in conjunction with its effectiveness – we are typically prepared to accept relatively more risk as benefit increases – we will continue to use the term benefit:risk balance.

In clinical trials, certainly to date, a descriptive approach is usually taken. Adverse events are typically reported by study investigators on the basis of their own observations (e.g., from a physical examination of a subject), or they are self-reported by a subject. Typical adverse events include dizziness, headache and nausea. Adverse events of special interest may also be monitored. If it is suspected from previous information (e.g., data for a previously marketed drug in the same chemical class as the investigational drug, or nonclinical safety signals) that the drug may cause a particular adverse event, this event may be monitored closely. The numbers of various adverse events are typically tabulated for each treatment group in the trial, both in absolute and percentage terms. (Percentage terms allow better comparison between groups when the numbers of participants in different treatment groups are not the same.) Serious adverse events are also documented. In addition, a narrative providing more detail for each serious adverse event is provided.

Occurrence of adverse events in the placebo treatment group indicates the “background rate” of these events. After a drug is approved, these occurrence rates provide physicians and patients with estimates of the likely occurrence of these events if the patient is not treated with the drug. The simple descriptive statistics that have often been used for safety data, both in regulatory applications and in an approved drug’s labeling, leave prescribing physicians to decide in an informal manner whether a difference in the occurrence of an adverse event between the drug treatment group and the placebo group is statistically
significant. That is, they are not provided with the results of formal inferential hypothesis testing that could have been conducted to determine if the occurrence of the adverse event differed between groups to a statistically significant degree.

One rationale that has typically been given for not conducting such statistical tests is the issue of multiplicity: If we conduct enough statistical tests, one (or more) of them is likely to provide a statistically significant result by chance alone. Since many different adverse events are recorded during a trial, performing an inferential test for each one would almost certainly provide some statistically significant results by chance alone. This outcome means that these particular results would be given much greater attention than they actually deserve. However, if appropriate care is taken, such as pre-specifying a small number of safety parameters of particular interest – the same approach that is taken for efficacy objectives – it is certainly possible to employ inferential statistical approaches in this context.

Given the critical importance of safety data, it is surprising that such approaches have not been used to a much larger degree. Statisticians, such as Robert O’Neill at the FDA (e.g., see O’Neill, 1998), have been advocating a more sophisticated approach to the analysis of safety data for many years (see Durham and Turner, 2008, for an introduction to such approaches). However, at this point, quantification of efficacy is arguably much more advanced than quantification of safety data. The absence of sufficient quantitative safety data leads to difficulties in the quantitative assessment of benefit:risk balances, which by definition requires quantification of both benefit (operationalized as efficacy data) and risk (operationalized as safety data). O’Neill addressed this issue recently in a very readable paper (O’Neill, 2008), discussing how to make progress in benefit:risk analysis of clinical trial data. I highly recommend this paper to you.

References


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