Chapter 16
Statistical Methods Applied in Drug Safety

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ABSTRACT

There are various statistical techniques used to quantitatively establish associations between drugs and suspected adverse effects. These associations between Drug Event Combinations (DEC) are clinically assessed to determine the potential safety issues.

Statistical techniques are currently applied to the analysis of AE counts in both pre-marketing clinical trials and post-marketing observational data. The objective in both areas is to detect AEs in the particular drug treatments. In pre-marketing clinical studies, statistical outcome helps to detect relative risks and compatibility ratios, whereas in post-marketing, it helps in calculating the disparity between the observed and expected values for a given drug-event combination.

This chapter introduces the commonly used statistical methods to analyze the safety issues within the DEC and explains their statistical interpretation for a better understanding of the readers.

INTRODUCTION

Clinical trials are usually conducted in four phases. Phase 1, 2, and 3 are conducted on human beings to assess one or more beneficial therapies. Evaluating safety profile of the drug is one of the key purposes of clinical studies. Outcome of the evaluation determines approval of new drugs by the regulatory authorities. After the drug is approved and used by the patients, adverse events are monitored through post marketing studies (Phase 4) / other epidemiological studies by regulatory agencies and international organization like FDA, MCA, WHO. After the analysis of the safety data from these studies, the regulatory authorities make recommendations, which may range from minor labeling changes to recall of the drug.

In order to monitor the benefits and risks of the medication, they count on few innovative tools and methods that can enhance the early detection and assessment of the adverse drug reactions.

The objective of this chapter is to provide a complete understanding of the popular statistical methods, which are commonly used to evaluate the signal detection in drug safety related problems.

DOI: 10.4018/978-1-4666-0309-7.ch016

BACKGROUND

Adverse Drug Reactions (ADR) are between the fourth and sixth leading cause of death in USA; fatality rate as a result of ADRs was estimated at 0.32% among hospitalized patients. The annual cost of ADR related hospital costs was estimated at $1.6-4 billion (Lazarou, et al., 1998; Bond, et al., 2006).

There were 31 safety-based FDA drug medications withdrawn between 1980 and 2007 (FDA, 2011).

The direct cost of a post approval drug withdrawal to a pharmaceutical company can exceed millions of dollars. On average, the investment needed to develop a drug is $1.1 billion and the development time is 15 years (NCBI, 2011). A withdrawal of a drug post-approval thus is huge financial loss. Add to this the potential legal costs and the negative impact that the brand suffers.

The primary goal of Phase 1 studies is to identify the Maximum Tolerable Dose (MTD) without toxicity and other adverse events. Although adverse effects are monitored and described, they cannot be precisely monitored in this phase as the number of subjects is small (Chevret, 2006; Edler, 2001; Rosenberger & Haines, 2002; O'Quigley, 1999, 2002; Ahn 1998). In pre-marketing clinical studies (Phase 2 and Phase 3), AE rates between the treatment and placebo-control arms of the study are the focus. Results are summarized with statistics, including Relative Risks (PRR) and Odds Ratios (OR). In post-marketing data, the number of subjects who are using the drugs of interest is typically unknown, and the same statistics cannot be calculated. As such, comparisons of AE rates between drugs typically use a score comparing the fraction of all reports for a particular event for a specific drug with the fraction of reports for the same particular event for all drugs. This analysis can be refined by adjusting for aspects of reporting or characteristics of the patient that might influence the amount of reporting. In addition, it may be possible to limit the analysis for drugs of a specific class, or for drugs that are used to treat a particular disease.

The statistic generated by the data mining techniques (BCPNN, EBGM, PRR, or OR) quantifies the disparity between the observed and expected values for a given DEC. The statistic is typically compared to a threshold. A potential excess of AEs is often defined as any DEC with a score exceeding the specified threshold (FDA, 2005).

Regulatory agencies like the FDA and International organizations like the WHO usually monitor the safety profile of all the drugs in their respective databases—which could mean analyzing thousands of possible AEs for thousands of drugs. No doubt, screening of large databases of the spontaneous case reports on possible AEs is cumbersome.

Therefore, they rely on very complex data mining techniques to facilitate signal detection.

In general, the commonly used statistical methods are:

- Bayesian Confidence Propagation Neural Network (BCPNN),
- Empirical Bayesian Geometric Mean (EBGM)
- Proportional Rate Ratio (PRR), and
- Odds Ratio (OR).

However, along with these statistical techniques, there are a whole lot of simple methods, which are also used concurrently to carry out trend analysis and stratification analysis. Techniques such as AE Method, Striking Case Method, and Reporting Rate Criteria can be used to carry such activities very efficiently.